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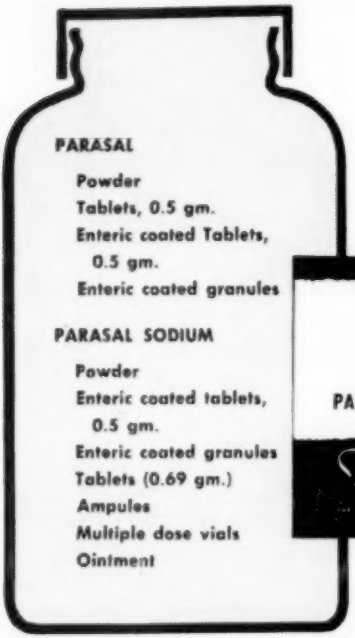

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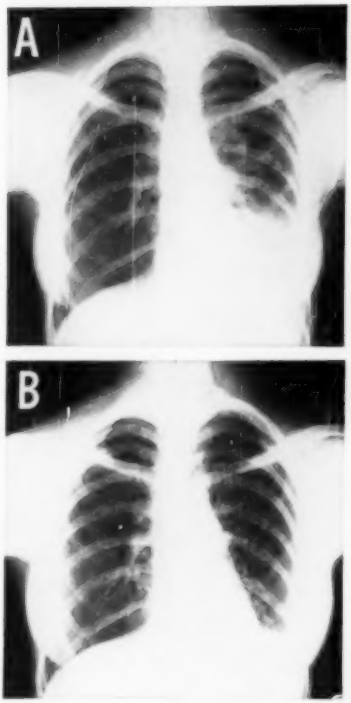

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PARA-AMINOSALICYLIC ACID TREATMENT IN PULMONARY TUBERCULOSIS

Comparison between 94 Treated and 82 Untreated Cases

THE THERAPEUTIC TRIALS COMMITTEE OF THE SWEDISH NATIONAL ASSOCIATION AGAINST TUBERCULOSIS[1]

(Received for publication October 14, 1949)

Introduction

In 1943, on the basis of studies made by Bernheim (1), Lehmann (2), and Rosdahl (3), investigations on para-aminosalicylic acid (Aminosalylum, PAS) were started, and soon after the production of PAS was begun at Ferrosan Research Laboratories in Malmö, Sweden. Clinical tests with PAS in treatment of pulmonary tuberculosis were started in March 1944 at the Renström Hospital in Gothenburg (Vallentin (4), Lehmann *et al.* (2b and 12)), and later in many other hospitals (Westergren (5), Stavenow (6), Alin and Difs (7), Carstensen and Sjölin (8), Dempsey and Logg (9), Erdei (10), Steinlin and Wilhelmi (11), and others). The largest study, 378 cases from six Swedish sanatoriums, has been reported by Vallentin, Törnell, Beskow, Carstensen, Thune, Helleberg, and Lehmann (12). Distinct clinical improvement after PAS treatment was noted in so great a percentage of the cases that para-aminosalicylic acid could be assumed to have some value as a remedy against tuberculosis. The account published of these investigations affords no direct information, however, as to how large a part of the noted improvement could be ascribed to PAS, and how large a part was due to other treatment given at the same time (sanatorium regimen, et cetera). Hence it was considered necessary to start an investigation in which a group of PAS-treated cases should be compared with a control group not given PAS but in all other respects treated in exactly the same way as the PAS group.

[1] The Committee for the Trial of Para-aminosalicylic Acid has the following members: C. Sigurd Backman (Head of Sjö-Gunnarsbo Sanatorium, Åsunden); Gösta Birath (Head of Tuberculosis Department II, Söderby Sjukhus, Uttran; Assistant Professor of Phthisiology, Karolinska Institutet, Stockholm); Torsten Bruce (Head of Tuberculosis Department I, Söderby Sjukhus, Uttran; Assistant Professor of Medicine, Karolinska Institutet, Stockholm); Leonard Goldberg (Associate Professor of Pharmacology, Karolinska Institutet, Stockholm); Bertil Karth (Head of Central Sanatorium, Västerås); Rolf Lemming (Head of Central Sanatorium, Arvika); Gunnar Lindgren (Head of Remedy Section, Royal Medical Board; Assistant Professor of Medicine, Medical Service, Serafimerlasarettet, Stockholm); and John Lundquist (Head of Tuberculosis Section, Royal Medical Board; General Secretary of the Swedish National Association against Tuberculosis).

Method

The investigation has been carried out in five Swedish sanatoriums. As soon as a patient was admitted, it was decided whether the case was suitable for testing the efficiency of PAS. One-half of the patients in this category were treated with PAS, and the other half were used as controls, the distribution of the cases on these two groups being determined by allotment.

All cases of miliary tuberculosis or tuberculous meningitis received streptomycin and were excluded from the study. Moreover, all patients with clinical symptoms of tuberculosis of the small intestine were excluded from the trial and the allotment, and were treated with PAS as soon as they had been admitted (8).

The physician in charge was not told whether a case was to be given PAS or would belong to the controls, and a placebo of the same appearance, smell, and acid taste as PAS granulate was distributed to the patients of the control group.

TABLE 1

Length of Test Period

Group	Test period (weeks)								Mortality		Total number of cases
	1-2	3-4	5-6	7-8	9-10	11-12	13-14	≧15	Absolute number	Per cent	
Number of cases treated with PAS		3	1			5		85	3	3.2	94
Number of controls		3	5	3		2		69	9	11.0	82

Three patients were discharged after a little more than two months' treatment, by their own request and against advice; two after 2.5 months on account of lack of accommodation. In 3 cases showing a very rapid deterioration, it was considered necessary to discontinue the trial after six weeks of test period and to change to another therapy. When computing the material it was found that all these 3 cases belonged to the controls. One case was given PAS for only two months, another for only one month, a pronounced alimentary discomfort caused by PAS having made it impossible to fulfill the treatment for three months. Twelve patients died during the test period. The difference, 7.8 ± 3.90 per cent, in the mortality between the PAS-treated cases and the controls is on the border of significance.

The PAS granulate[2] contained 70 per cent para-aminosalicylic acid and was varnished with shellac. This coating protects the material from the gastric juice for at least 30 minutes.

A total daily dose of 10 Gm. of para-aminosalicylic acid was given in individual doses of 5, 2, 2, and 5 Gm. of the granulate, administered with meals. For children the dose was decreased in proportion to weight. The chemotherapy was continued for a total period of three months. In a few cases (12 per cent of the total number), however, the treatment had to be discontinued earlier (table 1).

Before starting treatment, a detailed examination of each patient was carried out, including temperature and weight determinations, chest roentgenograms, erythrocyte sedimentation rates, differential leukocyte counts, measurements of sputum volume, and search for tubercle bacilli in smears of sputum.

[2] Manufactured by Ferrosan Ltd., Malmö, Sweden.

During the test period, roentgenograms were taken once a month and the sputum volume was measured daily. The other examinations were repeated at intervals of no longer than 14 days.

Statistical Methods

σ = standard deviation = $\sqrt{\frac{s(x - \bar{x})^2}{n - 1}}$ (1)

Standard error ($\mathfrak{S}_M$) of mean (M): $\mathfrak{S}_M = \frac{\sigma}{\sqrt{n}}$ (2)

n = number of variates
$S(\ )$ = sum of $\cdots$
x = variate
$\bar{x}$ = average of variates = $\frac{S(x)}{n}$

Standard error of difference ($\mathfrak{S}_\Delta$) between means (M_1, M_2) = $\mathfrak{S}_\Delta = \sqrt{\mathfrak{S}^2_{M_1} + \mathfrak{S}^2_{M_2}}$ (3)

Significance is tested by using Student's t with the appropriate number of degrees of freedom according to ordinary formulas (13).

X-value: Comparison of two *series* of means, i.e., a sequence of means from the control group (M_1, $M_2 \cdots$) and a sequence of means from the PAS group (M_1'', $M_2'' \cdots$), was performed in the following way:

The differences (Δ_1, Δ_2, $\cdots$) between corresponding means from each series ($\Delta_1 = M_1^1 - M_1''$; $\Delta_2 = M_2^1 - M_2'' \cdots$) were computed, the corresponding t-values of the differences ($t_{\Delta_1} = \frac{\Delta_1}{\mathfrak{S}_{\Delta_1}}$; $t_{\Delta_2} = \frac{\Delta_2}{\mathfrak{S}_{\Delta_2}} \cdots$) were added, and were divided by $\sqrt{N}$, where N is the number of differences Δ_1, $\Delta_2 \cdots \Delta_N$.

The resulting value, denoted by X, will approximately be normally distributed (14) with the standard deviation 1. Its significance is tested as an ordinary Student's t with an infinite number of degrees of freedom under the assumption that the differences (Δ_1, $\Delta_2 \cdots$) are distributed at random.

Computation of rectilinear regression line, regression coefficient, analysis of covariance, et cetera, were performed according to ordinary formulas (13, 15).

Standard error of percentage $\mathfrak{S}_p = \sqrt{\frac{p(100 - p)}{n}}$ (4)

Standard error of difference between two percentages $\mathfrak{S}_{P_1P_2} = \sqrt{\mathfrak{S}^2_{P_1} + \mathfrak{S}^2_{P_2}}$ (5)

Significance tested by Student's t for an infinite number of degrees of freedom ($n > 50$).

Comparison of percentages ($n < 50$), tests of homogeneity and heterogeneity, agreement between distributions, et cetera, were performed by χ^2 – analysis according to ordinary formulas (13).

Levels of significance (in accordance with Cramér):
The 5 per cent level ($P = 0.05 - 0.01$) = almost significant
1 per cent ($P = 0.01 - 0.001$) = significant
0.1 per cent ($P < 0.001$) = highly significant.

Clinical Material

The distribution of the material according to types of tuberculosis is given in figure 1 and according to sex and age in figure 2. As expected, the distributions in the PAS and the control group are in good agreement, the random probability being > 0.3.

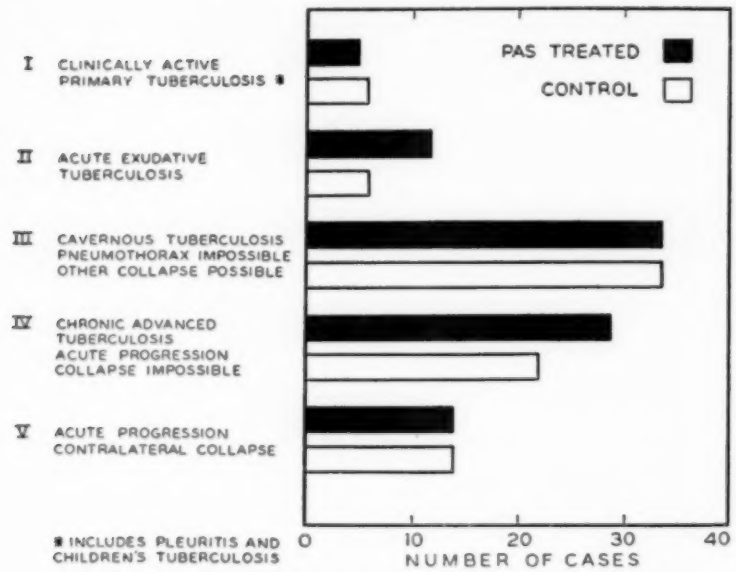
I CLINICALLY ACTIVE PRIMARY TUBERCULOSIS *
II ACUTE EXUDATIVE TUBERCULOSIS
III CAVERNOUS TUBERCULOSIS PNEUMOTHORAX IMPOSSIBLE OTHER COLLAPSE POSSIBLE
IV CHRONIC ADVANCED TUBERCULOSIS ACUTE PROGRESSION COLLAPSE IMPOSSIBLE
V ACUTE PROGRESSION CONTRALATERAL COLLAPSE
* INCLUDES PLEURITIS AND CHILDREN'S TUBERCULOSIS
PAS TREATED
CONTROL
0 10 20 30 40
NUMBER OF CASES

FIG. 1 Cases in study, classified by category of pulmonary tuberculosis

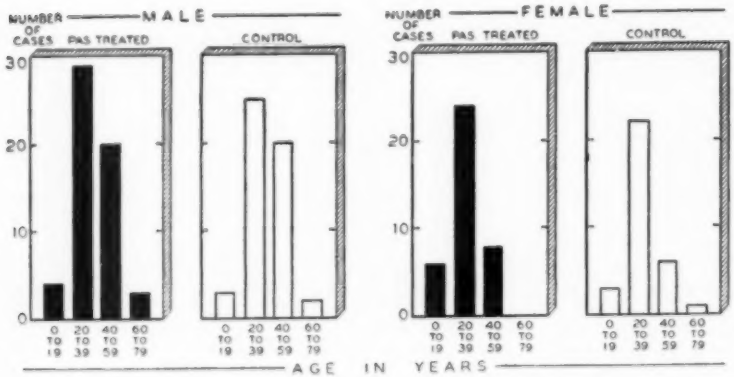

FIG. 2. Cases in study, classified by sex and age

RESULTS

Temperature: With regard to temperature, the cases have been divided into three groups: (a) 50 cases afebrile (< 37.0°C.) at beginning of treatment; (b) 54 cases with initial temperature of 37.0° to 37.3°C.; and (c) 72 cases with a higher initial temperature (figure 3). The fourth section of figure 3 includes all the cases

of the series as a whole, regardless of temperature at the beginning of the experiment.

The average temperature per period of three weeks has been calculated for each patient, i.e., average of 42 measurements. The means of these averages within each group are plotted in figure 3, ● indicating PAS-treated cases and □ controls. From the standard errors of these means ($\mathfrak{S}_M$), the standard errors ($\mathfrak{S}_\Delta$) of the differences between the means of the PAS and the control group within each three-week period have been ascertained. The lower border of the shaded area in figure 3 indicates a distance $= 2\frac{1}{2} \times \mathfrak{S}_\Delta$ from the means in the control group. Hence it is possible to read directly from the diagram when the difference between the PAS and the control group means becomes statistically significant.

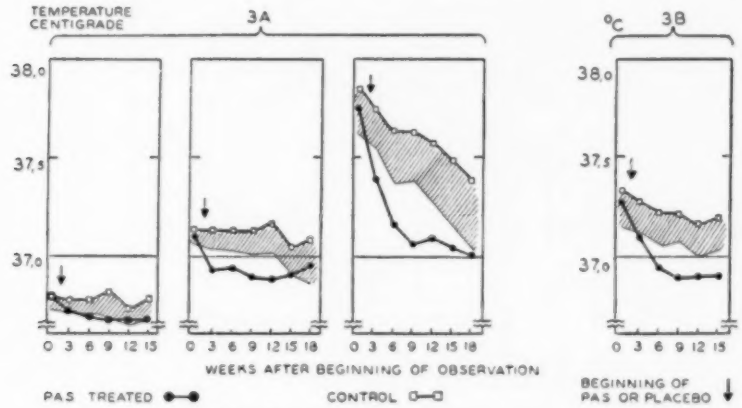

FIG. 3A FIG. 3B

FIG. 3A. Temperature trends for cases classified by initial temperature grouping
FIG. 3B. Temperature trend

This occurs among the cases with initial temperatures ≧ 37°C. very soon after PAS treatment has been started.

In the group consisting of all the cases in the series, regardless of the temperature at the beginning of the experiment, an X-value of 8.7 was computed. Hence the difference between the series of means of the PAS group and that of the controls is highly significant ($p < 0.001$).

Erythrocyte sedimentation rate (ESR): The erythrocyte sedimentation rate was determined according to Westergren. The results (fall in millimeters in one hour) which are summarized in figure 4 have been obtained as follows. Within every period of 14 days, starting from the beginning of the experiment, the average of the ESR determinations made during that period for each patient has been calculated. From these averages, group means for every period of 14 days have been computed and inserted in the diagram. The standard error ($\mathfrak{S}_\Delta$) of the differences between the means thus obtained has been calculated in the same way

as stated above. The area within a distance of $2\frac{1}{2} \times \delta_\Delta$ from the means of the control group has been shaded.

From figure 4 it will be seen that as early as two to three weeks after PAS treatment was begun the difference between the mean values of the PAS and the control group became significant.

The high mean values of ESR at the start of the experiment disclose a considerable degree of clinical activity of the tuberculosis in the cases included in the

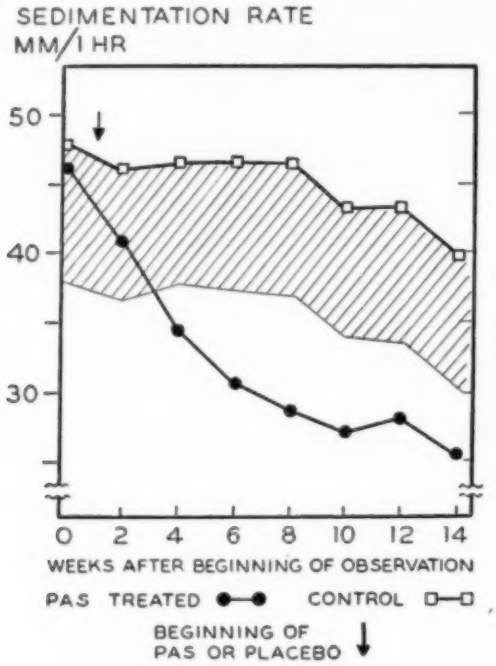

FIG. 4. Sedimentation rate trend

material. More than one-half of the material had an initial value of ESR exceeding a 40-millimeter fall in one hour.

A highly significant difference between the series of means of the PAS group and that of the controls ($p < 0.001$) was found, X being 9.2.

Gain in weight: Each patient was weighed once every two weeks. The gain in weight, counted from the beginning of the experiment, was calculated for each period of two weeks. The means of these values have been inserted in figure 5. From 615 individual values among cases treated with PAS and 505 in the control group, two regression lines were calculated. In the PAS group the average

[3] Regr. eq. $y = 0.18\,x - 0.365$; (y = gain in weight in Kg.; x = week).

gain in weight per week was 0.18 ± 0.022 Kg.[3], and in the control group 0.04 ± 0.035 Kg.[4] The difference, 0.14 ± 0.041 Kg., is highly significant ($p < 0.001$).

Differential count: Differential count of white blood corpuscles was done at least once every two weeks and the percentage of stab[5] cells and lymphocytes noted (figures 6A and B). The dots in the diagram indicate means within each period of two weeks, and have been obtained in the same way as the correspond-

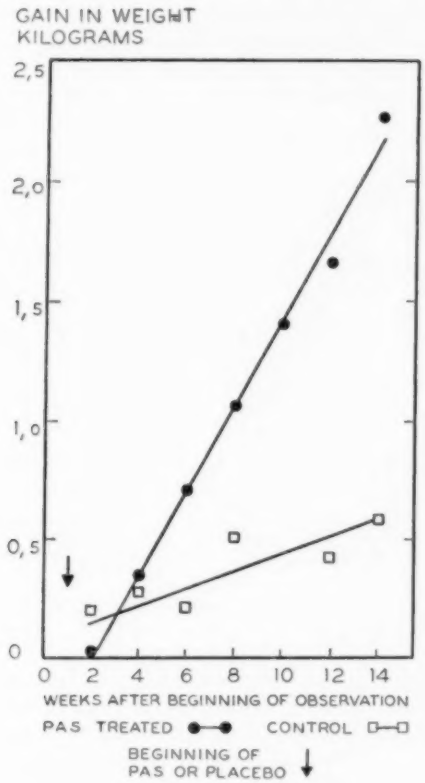

FIG. 5. Weight trend

ing ESR mean values. The standard error ($\mathfrak{S}_\Delta$) of the differences between the means mentioned above has been calculated in the usual way. The area within a distance of $2\frac{1}{2} \times \mathfrak{S}_\Delta$ from the means of the control group has been shaded. It can be seen from the diagram (figure 6) that within a month after beginning treat-

[4] Regr. eq. $y = 0.04\,x + 0.104$.

[5] Immature polymorphonuclear leukocytes.

ment the differences between the means of the PAS and the control group become significant.

The values of X, 9.9 for stab cells and 4.7 for lymphocytes, indicate a significant difference between the series of means of the PAS and control groups ($p < 0.001$).

Sputum: The *volume of sputum* in milliliters was measured daily. For each patient an average was calculated for every period of two weeks and the means of these averages within the PAS and the control group are indicated in figure 7A. The standard errors of the differences between the means have been obtained in the same way as those given above. Also in other particulars the indications are the same as in figures 3, 4, and 6.

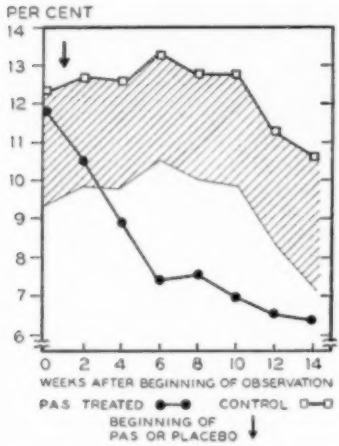

FIG. 6A

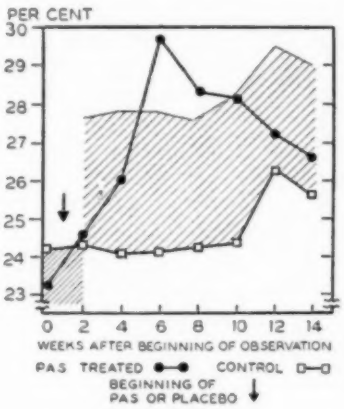

FIG. 6B

FIG. 6A. Trend of immature leukocytes (stab cells) in differential count
FIG. 6B. Trend of lymphocytes in differential count

Smears were examined with regard to their *content of acid-fast bacilli* at least once every two weeks, usually more often. In each of the two groups, PAS-treated cases and controls, and during each period of two weeks the number of smears containing acid-fast bacilli was determined. The values obtained are given in figure 7B as percentages of the total number of smears examined during each of the same periods.

The thin border line of the shaded area in the diagram indicates a distance of $2\frac{1}{2} \times \delta_\Delta$ from the control group percentages. A significant difference between the values of the PAS and the control group is observed after only two weeks of treatment.

In evaluating the efficacy of PAS, it was found to be inadvisable to use the time from the beginning of chemotherapy to the time when smears from the patient's sputum consistently failed to reveal acid-fast bacilli because, as the patient's

condition improved, most of the smears alternated several times from positive to negative, and vice versa.

Calculation of X was made for volume of sputum as well as for presence of acid-fast bacilli in smears. The values obtained, 5.9 and 13.9, indicate in both respects highly significant differences between the series of means of the PAS and control groups ($p < 0.001$).

Roentgenograms: Roentgenographic examinations of the chest were made at the beginning of the test period and then at intervals of one month.

Five of the investigators examined the roentgenograms (Backman, Birath, Bruce, Karth, and Lemming). Improvement was indicated by the designations plus 1 to plus 3; deterioration, by minus 1, minus 2, or minus 3; plus 3 indicated

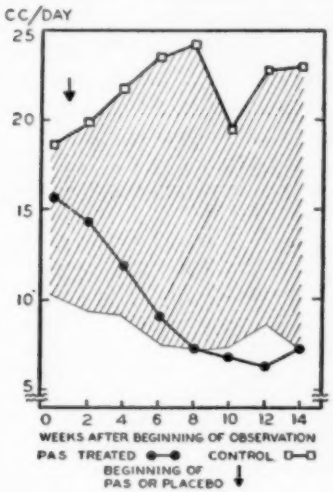

FIG. 7A

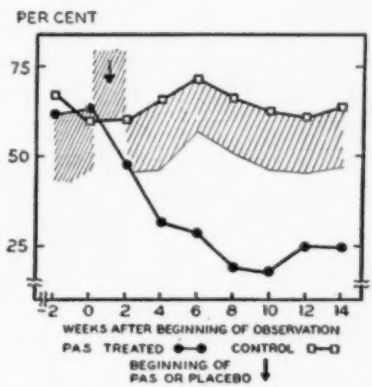

FIG. 7B

FIG. 7A. Sputum volume cc. per day
FIG. 7B. Percentage of smears containing tubercle bacilli

maximum improvement and minus 3, maximum deterioration during the test period. For each patient, the average was calculated of the values arrived at by those four physicians who had neither seen that particular patient nor known whether he belonged to the PAS or the control group. These averages were then used in plotting figure 8.

To settle the degree of agreement between different examiners the following calculations were made. For every case studied the individual examiners's opinion was expressed as indicated above. The difference between this figure and the average of the figures given by the three others was calculated. The average of these differences and its standard error were computed for each of the five examiners who had judged the roentgenograms. The following averages of the

differences were obtained: −0.02, −0.03, −0.13, +0.06, +0.14. Each of the values given is the average of at least 120 and at most 152 differences and has a standard error of 0.06; hence the differences are not greater than could have been caused by mere chance (table 2). The numerical values −0.13 and +0.14 are too small to play any role; the figures assigned by an examiner being one or multiples of one.

Hence the opinions of the different examiners of the effect of treatment discernible in the roentgenograms coincided extremely well in individual cases, in spite of the fact that each one made his examination and gave his opinion with no knowledge of the result arrived at by the others. Consequently, when calculating the average mentioned above, no correction was necessary.

Figure 8 illustrates that within the PAS group (upper part of figure) only 6 cases (7 per cent) have deteriorated as judged by the roentgenograms, while among the controls (lower part of figure) not less than 33 cases (43 per cent) have deteriorated. The difference is highly significant. ($\chi^2 = 103$ [3 degrees of freedom]; $p < 0.001$).

TABLE 2

Mean Differences between the Opinion Expressed by Every Single Examiner and the Average Opinion of the Three Other Examiners Judging the Roentgenograms of the Same Cases

EXAMINER	MEAN DIFFERENCE ± STANDARD ERROR	n	t	p
Ba	−0.02 ± 0.06	152	0.35	>0.7
Bi	−0.03 ± 0.06	142	0.48	>0.6
Br	−0.13 ± 0.05	121	2.41	>0.01
K	+0.14 ± 0.06	145	2.54	>0.01
L	+0.06 ± 0.06	120	0.98	>0.3

THE EFFICIENCY OF PAS TREATMENT IN DIFFERENT TYPES OF PULMONARY TUBERCULOSIS

In order to obtain a conception of the extent to which PAS is effective in different types of tuberculosis, the material was divided into the five categories shown in figure 1. For each month of treatment, means of ESR, gain in weight, sputum volume, temperature, and percentage of stab cells and lymphocytes in differential count, as well as percentage of smears containing acid-fast bacilli, were calculated, the same procedure being used as previously when determining the means for each two or three weeks' period. The results of the roentgenographic examinations were also given for the five categories.

Figure 9 shows that in clinically active primary tuberculosis (type I) a spontaneous tendency towards regression is noted in all examinations. However, the cases treated with PAS have improved throughout more quickly.

In type II, acute exudative tuberculosis, the control group showed a definite tendency towards deterioration, with the exception of ESR and temperature. The loss of weight was very rapid. The course of the disease in the cases treated with PAS is considerably more favorable.

In cavernous tuberculosis where attempts at pneumothorax treatment had not succeeded, but where the clinical condition might permit other forms of collapse therapy (type III), the control group is rather stationary (except for gain in weight). The favorable effect of PAS is apparent and highly significant.

In chronic advanced tuberculosis with acute progression where the clinical condition does not allow any form of collapse therapy (type IV), the control group shows a progressive loss in weight during the time of observation, but in

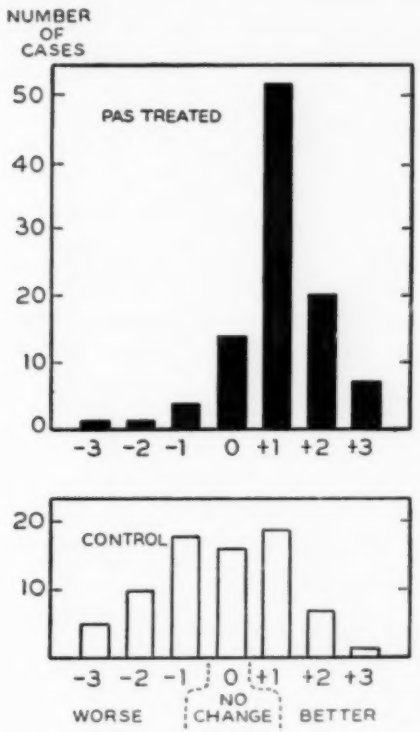

FIG. 8. Cases in study, classified by roentgenographic change

other respects is fairly stationary. The effect of PAS is found to be highly significant as to ESR, sputum amount, percentage of smears containing acid-fast bacilli, percentage of stab cells in differential count, and temperature. In other respects a significant effect is obtained.

In acute progression, in cases with contralateral collapse treatment (type V), a stationary condition or a slight tendency towards improvement is found in the control group. PAS has a highly significant effect on ESR, percentage of

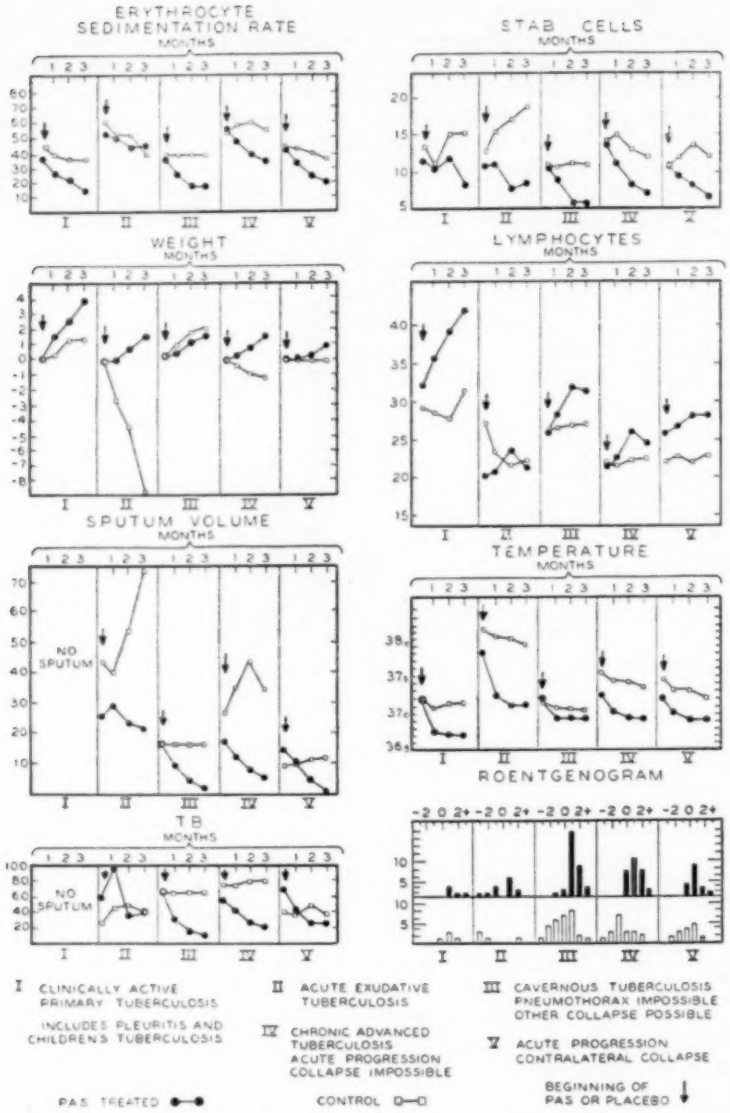

FIG. 9. The efficiency of PAS in different types of pulmonary tuberculosis

smears containing acid-fast bacilli, differential count, and temperature; the difference between the two groups in regard to sputum volume is significant.

Summary

One group of 94 cases of active pulmonary tuberculosis was treated with para-aminosalicylic acid (10 Gm. daily) for three months, while another group of 82 similar cases served as controls. Assignment into the two groups had been allotted from a total of 176 patients selected for the therapeutic test. Temperature, sputum amount, erythrocyte sedimentation rate, weight, differential count, and content of acid-fast bacilli in smears of sputum were analyzed at regular intervals during the test period. Pulmonary roentgenograms were taken every month. In all respects the patients treated with para-aminosalicylic acid improved considerably more rapidly than patients in the control group, and the results are statistically significant.

Sumario

El Acido Para-Aminosalicílico en el Tratamiento de la Tuberculosis Pulmonar: Comparación entre 94 Casos Tratados y 82 no Tratados con el Mismo

Un grupo de 94 casos de tuberculosis pulmonar activa fué tratado con ácido para-aminosalicílico (10 gramos diarios) durante tres meses, en tanto que otro grupo de 82 casos semejantes sirvió de testigo. Para la división en los dos grupos se tomó un total de 176 enfermos escogidos para la prueba terapéutica. Durante el período de estudio, se analizaron periódicamente la temperatura, la cantidad de esputo, el índice de eritrosedimentación, el peso, fórmula leucocitaria y contenido de bacilo ácidorresistentes en frotes de esputo. También se tomaron cada mes radiografías pulmonares. En todos sentidos, los sujetos tratados con ácido para-aminosalicílico mejoraron considerablemente con mayor rapidez que los testigos, y el resultado posee importancia estadísticamente.

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APPENDIX

Statistical Table A

	WEEK	PAS-TREATED CASES		CONTROL GROUP		DIFFERENCE
		$M \pm \varepsilon_M$	n	$M \pm \varepsilon_M$	n	$\Delta \pm \varepsilon_\Delta$
Temperature (°C.)	0	36.79 ± 0.025	26	36.80 ± 0.024	24	0.01 ± 0.035
	3	36.72 ± 0.024	26	36.78 ± 0.027	24	0.06 ± 0.036
	6	36.70 ± 0.025	26	36.78 ± 0.030	24	0.08 ± 0.039
	9	36.67 ± 0.030	26	36.84 ± 0.047	24	0.17 ± 0.056
	12	36.68 ± 0.025	25	36.73 ± 0.025	24	0.05 ± 0.035
	15	36.67 ± 0.032	15	36.79 ± 0.038	12	0.12 ± 0.050
	0	37.12 ± 0.020	31	37.14 ± 0.023	23	0.02 ± 0.031
	3	36.93 ± 0.037	31	37.14 ± 0.031	23	0.21 ± 0.048
	6	36.95 ± 0.032	30	37.14 ± 0.038	23	0.19 ± 0.050
	9	36.90 ± 0.027	29	37.14 ± 0.043	23	0.24 ± 0.051
	12	36.88 ± 0.030	29	37.17 ± 0.050	22	0.29 ± 0.058
	15	36.92 ± 0.037	24	37.06 ± 0.045	18	0.14 ± 0.058
	18	36.97 ± 0.066	18	37.09 ± 0.068	13	0.12 ± 0.095
	0	37.76 ± 0.060	37	37.87 ± 0.076	35	0.11 ± 0.097
	3	37.38 ± 0.049	37	37.75 ± 0.076	35	0.37 ± 0.090
	6	37.13 ± 0.045	37	37.63 ± 0.099	33	0.50 ± 0.109
	9	37.07 ± 0.049	36	37.62 ± 0.091	31	0.55 ± 0.103
	12	37.09 ± 0.059	35	37.57 ± 0.112	28	0.48 ± 0.127
	15	37.03 ± 0.052	33	37.50 ± 0.121	26	0.47 ± 0.132
	18	37.00 ± 0.066	26	37.39 ± 0.120	20	0.39 ± 0.137
	0	37.28 ± 0.049	94	37.35 ± 0.062	82	0.07 ± 0.079
	3	37.10 ± 0.036	94	37.30 ± 0.058	82	0.20 ± 0.068
	6	36.95 ± 0.029	93	37.23 ± 0.059	80	0.28 ± 0.066
	9	36.90 ± 0.028	91	37.24 ± 0.055	78	0.34 ± 0.062
	12	36.91 ± 0.030	89	37.18 ± 0.061	74	0.27 ± 0.068
	15	36.92 ± 0.031	72	37.21 ± 0.070	56	0.29 ± 0.077
Erythrocyte sedimentation rate (mm./1 hr.)	0	45.8 ± 2.46	92	47.4 ± 3.14	80	1.6 ± 3.89
	2	40.7 ± 2.40	93	46.0 ± 2.94	82	5.3 ± 3.79
	4	34.3 ± 2.36	91	46.2 ± 2.57	81	11.9 ± 3.49
	6	30.6 ± 2.25	91	46.1 ± 2.87	79	15.5 ± 3.64
	8	28.6 ± 2.16	91	46.2 ± 3.16	75	17.6 ± 3.83
	10	27.1 ± 2.31	90	43.2 ± 3.09	73	16.1 ± 3.86
	12	27.8 ± 2.47	87	43.1 ± 3.08	70	15.3 ± 3.95
	14	25.3 ± 2.26	79	39.4 ± 2.99	67	14.1 ± 3.75

n = number of cases examined.

Statistical Table B

	WEEK	PAS-TREATED CASES		CONTROL GROUP		DIFFERENCE
		$M \pm \varepsilon_M$	n	$M \pm \varepsilon_M$	n	$\Delta \pm \varepsilon_\Delta$
Gain in weight, (Kg.)	2	0.03 ± 0.085	92	0.20 ± 0.140	82	0.17 ± 0.164
	4	0.35 ± 0.152	92	0.30 ± 0.216	79	−0.05 ± 0.245
	6	0.71 ± 0.194	91	0.21 ± 0.295	77	−0.50 ± 0.354
	8	1.05 ± 0.227	90	0.51 ± 0.380	71	−0.54 ± 0.443
	10	1.40 ± 0.262	89	0.45 ± 0.456	69	−0.95 ± 0.526
	12	1.67 ± 0.306	86	0.43 ± 0.504	67	−1.24 ± 0.590
	14	2.29 ± 0.351	75	0.56 ± 0.610	60	−1.73 ± 0.704
Per cent stab cells in differential count	0	11.86 ± 0.82	94	12.38 ± 0.88	82	0.52 ± 1.20
	2	10.55 ± 0.75	94	12.72 ± 0.86	81	2.17 ± 1.14
	4	8.99 ± 0.66	91	12.60 ± 0.90	80	3.61 ± 1.12
	6	7.46 ± 0.52	91	13.31 ± 0.97	77	5.85 ± 1.10
	8	7.54 ± 0.61	90	12.79 ± 0.91	76	5.25 ± 1.10
	10	6.96 ± 0.48	90	12.73 ± 1.05	71	5.77 ± 1.15
	12	6.56 ± 0.46	88	11.25 ± 1.03	72	4.69 ± 1.13
	14	6.37 ± 0.73	70	10.60 ± 1.11	58	4.23 ± 1.33
Per cent lymphocytes in differential count	0	23.19 ± 0.94	94	24.21 ± 1.07	81	1.02 ± 1.42
	2	24.51 ± 0.92	94	24.30 ± 0.95	80	−0.21 ± 1.32
	4	26.60 ± 1.14	92	24.11 ± 0.94	79	−2.49 ± 1.48
	6	29.66 ± 1.13	90	24.10 ± 0.89	77	−5.56 ± 1.44
	8	28.23 ± 0.93	90	24.18 ± 0.95	77	−4.05 ± 1.33
	10	28.14 ± 1.02	90	24.36 ± 1.17	72	−3.78 ± 1.55
	12	27.13 ± 1.05	88	26.18 ± 0.80	71	−0.95 ± 1.32
	14	26.55 ± 1.24	66	25.64 ± 1.35	56	−0.91 ± 1.83
Sputum volume, (ml./day)	0	16.05 ± 2.32	84	18.83 ± 3.64	77	2.78 ± 4.32
	2	14.53 ± 2.06	91	19.75 ± 3.62	81	5.22 ± 4.16
	4	12.09 ± 1.79	92	21.85 ± 4.74	80	9.76 ± 5.08
	6	9.34 ± 1.77	89	23.48 ± 6.15	77	14.14 ± 6.39
	8	7.34 ± 1.88	88	24.38 ± 6.63	76	17.04 ± 6.90
	10	6.83 ± 1.70	87	19.37 ± 4.43	71	12.54 ± 4.75
	12	6.40 ± 1.69	82	22.81 ± 5.36	68	16.41 ± 5.62
	14	7.46 ± 2.28	67	23.07 ± 5.85	61	15.61 ± 6.26
Percentage of smears containing tubercle bacilli	0	62.2 ± 5.35	55	59.7 ± 5.59	51	−2.5 ± 7.73
	2	48.2 ± 3.85	86	60.0 ± 4.38	69	11.8 ± 5.83
	4	32.3 ± 5.85	80	65.0 ± 4.30	70	32.7 ± 7.26
	6	28.7 ± 3.69	75	70.5 ± 4.18	66	41.8 ± 5.57
	8	18.9 ± 3.27	76	65.6 ± 4.64	61	46.7 ± 5.67
	10	18.0 ± 3.26	74	61.5 ± 5.10	54	43.5 ± 6.05
	12	24.5 ± 3.60	76	60.4 ± 5.13	51	35.9 ± 6.26
	14	24.3 ± 4.23	65	63.6 ± 5.48	46	39.3 ± 6.92

n = number of cases examined.

PARA-AMINOSALICYLIC ACID (PAS) IN PULMONARY AND EXTRAPULMONARY TUBERCULOSIS[1]

BO CARSTENSEN

(Received for publication November 29, 1949)

Since January 1947 more than 300 cases of pulmonary tuberculosis have been treated with para-aminosalicylic acid (PAS), either at Sandträsk Sanatorium (January to August 1947) or, since September 1947, at Solliden Sanatorium. In about 100 of these cases PAS has been used in combination with streptomycin. Although the observation period is too short to permit final conclusions regarding the effect of PAS, the number of cases is large enough to give some valuable information.

MATERIAL AND METHODS

During the first twenty months of the investigation the patients selected for PAS treatment fulfilled the following requirements:

1. The diagnosis of tuberculosis was confirmed by a positive culture or guinea pig test shortly before the treatment or by a typical roentgenographic picture and the finding of acid-fast bacilli in a smear of sputum.
2. The pulmonary process was progressive or stationary, but was not improving.
3. The disease was far advanced or moderate (exudative as well as proliferative types) with or without extrapulmonary tuberculosis.
4. The observation period with bed rest and ordinary sanatorium regimen before treatment was at least two months in most cases.
5. Collapse treatment was allowed and not considered to interfere with the estimation of the PAS effect if (a) the pneumothorax treatment had been abandoned at least four months before the PAS treatment; or (b) the collapse therapy had been instituted at least four months before PAS and the process still showed signs of progression. The collapse therapy was continued during the treatment. No form of collapse therapy was initiated during PAS treatment.

In 5 of the 150 cases reported in table 1, exceptions to the stated procedure on collapse therapy had to be made owing to severe complications. Moreover, in 37 cases it was necessary to make exceptions to the rule on pretreatment observation because of the acute and extensive nature of the pulmonary process and/or severe complications. In 21 of these cases the observation period was less than one month; in 16 cases it was one to two months.

The patients received PAS or its sodium salt orally, 10 to 18 Gm. per day divided into 5 to 7 equal doses from 7 a.m. to 10 p.m.

The PAS preparation used at Solliden Sanatorium is a special form of enteric-coated granules.[2] Experiments which will be published subsequently have shown that various coatings may reduce or eliminate gastric disturbances due to PAS. In addition, the blood levels of PAS vary with the coating, i.e., possibly by influencing the absorption of the drug.

[1] From Solliden Sanatorium, Östersund, Sweden.

[2] Manufactured by Ferrosan Ltd., Malmö, Sweden.

RESULTS

In table 1 may be seen the findings and results[3] in 150 patients treated with PAS alone between September 1947 and August 1948. The excellent effects on the clinical status of the patients, and the laboratory tests are shown in the table.

TABLE 1

Preliminary Results as of November 1948 in 150 Cases of Pulmonary Tuberculosis Treated with PAS Alone, September 1947 to August 1948

	NUMBER OF CASES	IMPROVED			UNCHANGED	WORSE
General condition	150[1]		99		46	5
Weight	150[2]		109		27	14
Temperature	70	Afebrile 47	57	Reduction 10[3]	12	1
ESR 15	117		83[4]		28	6
Bronchitis	117	Disappeared 41	106	Decreased 65	11	—
Sputum	112	Disappeared 31	98	Decreased 67	14	—
Bacilli	117	Negative[5] 37	58	Decreased 21[6]	58	1
Gastrointestinal symptoms	26	Disappeared 18	25	Decreased 7	1	—
Roentgenogram: Exudative infiltrations	95	Disappeared 5		Regression 74	10	6
Roentgenogram: Proliferative infiltrations	105	—		10	94	1
Roentgenogram: Cavities	128	22[7]		50	48	8
Roentgenogram: Out of these tension cavities	10	5[7, 8]		1	4	—

[1] Fair condition in 53 cases of these before treatment
[2] Gain in body weight at least 2 Kg.
[3] In 9 cases of these below 37.5°C., in the tenth, below 37.8°C.
[4] ESR in 31 cases of these, <10; in 33 cases, 10 to 30; in 17 cases, <30 mm.
[5] Negative for 3 months by weekly examinations
[6] Positive smears less frequent
[7] Tomogram negative
[8] Average observation period before treatment: 15 months.

The favorable effect of PAS on patients with fresh, exudative, pulmonary lesions is well known by those who have used it and has been described earlier (1, 2, 3, 4). In more chronic, nodular forms of pulmonary tuberculosis and in tuberculosis

[3] This survey was compiled in collaboration with Dr. Gunnar Smårs.

of the larynx and bronchi good results are also achieved (3, 5, 6). Still better results sometimes may be seen with a combination of PAS and streptomycin (5, 7).

Twenty-two patients showed cavity closure during PAS treatment (see table 1). In addition, a number of cavities later showed closure roentgenographically, when PAS was supplemented with streptomycin. A follow-up study in August 1949 revealed that among these 22 cases, 8 patients had reappearance of their cavities. Six patients had received collapse treatment more than four months before PAS treatment, and one during the treatment. Roentgenograms of these patients showed no evidence of cavitation.

Thus, among 128 patients with cavitation, only 7 of those who received PAS treatment alone showed cavity closure one year after treatment.

A follow-up study in September 1949 of the 150 cases in table 1 is shown in table 2. These results are to be regarded as preliminary. Several of the patients designated as unimproved or as in relapse will receive collapse treatment as soon as their condition permits.

TABLE 2

Follow-up Study September 1949 of the 150 Cases Reported in Table 1

APPARENTLY CURED	ARRESTED	ACTIVE			OPERATIONS			DEAD
		Improved	Unimproved	Relapses	Thoracoplasty	Pneumothorax	Pulmectomy lobectomy	
33	8	15	15	7	49*	6	4	14*

* One thoracoplasty patient operated upon at another hospital, who died from a nontuberculous complication, is reported both in the thoracoplasty and the dead column.

Comment

Judging from reports in the literature and from our own experience regarding chemotherapy of pulmonary tuberculosis, it seems possible to draw the following conclusions.

PAS therapy alone is generally not sufficient for permanent closure of cavities. Collapse treatment is still necessary.

In fresh, exudative, pulmonary tuberculosis, PAS therapy is extremely valuable in rendering collapse treatment (pneumothorax or thoracoplasty) possible later on. Favorable results are also seen in patients with extensive lesions of a pneumonic type, who before the era of chemotherapy would have been considered hopelessly ill. However, early treatment is important.

Even in chronic, cavernous pulmonary tuberculosis with acute exacerbations, with complications and poor general condition, PAS therapy supported by the "strategic use of short courses of streptomycin," often produces sufficient improvement to render subsequent collapse treatment possible and effective.

Chemotherapy should always be used to prevent postoperative dissemination and complications when collapse treatment is instituted. Our results further suggest that a preparatory course of PAS treatment should be given a long time before collapse therapy and for some time postoperatively. For this reason, during the past year, all patients on

collapse therapy at Solliden Sanatorium have received prophylactic chemotherapy. Since December 1947, there has not been a single new case of tuberculous empyema following pneumothorax. Preventive chemotherapy is recommended for all elective procedures, e. g., bronchoscopy, nephrectomy, tonsillectomy in the presence of tuberculosis of the tonsils, et cetera.

The effect of PAS in human tuberculosis and in experimental tuberculosis is similar to that of streptomycin as are also the indications. Streptomycin acts more rapidly and should, therefore, be given in serious, acute forms of tuberculosis. Streptomycin treatment should always be combined with PAS since clinical and experimental experience (7, 9, 10, 11, 12, 13, 14) indicates that the combination is more effective than either drug alone. It is probable that the combination prevents or delays the emergence of resistance to streptomycin and possibly also to PAS (12, 13).

TABLE 3

Sensitivity to PAS, Expressed as Maximal Concentration of PAS in Mg. per 100 Ml. of Medium Which Permitted Growth of Tubercle Bacilli

(No sensitivity tests were performed before the treatment with PAS)

PATIENT NUMBER	PAS, DURATION OF TREATMENT, DAYS, AT DETERMINATION OF SENSITIVITY	PAS SENSITIVITY*
		After treatment
1	289	1.5
2	299	1.5
3	435	1.5
4	314	15
5	365	1.5
6	184	1.5
7	193	15
8	389	15
9	238	15
10	326	15
11 to 79		0.00015 to 0.015

* Maximal concentration of PAS in milligrams per 100 ml. of medium which permitted growth.

Unless it is possible to attain cavity closure by collapse treatment, streptomycin should not be used in chronic cavernous tuberculosis, since in such cases drug resistance is common and appears early. PAS is preferable in these cases, supplemented in certain cases by short courses of streptomycin.

In cavernous tuberculosis, bacterial resistance to streptomycin is seen as early as in the fourth week of treatment. PAS resistance has not appeared earlier than five to six months (*vide infra*). Among our own cases, where PAS sensitivity was determined[4] (79 cases up to August 1, 1949), five strains have shown resistance to 15 mg. of PAS per 100 ml. of medium and an additional 5 strains to 1.5 mg. of PAS per 100 ml. of medium. The shortest period of PAS therapy resulting in drug resistance was 184 days (table 3). This is in accordance with the results reported from the Mayo Clinic (15) where, among 73 PAS-treated cases in which drug sensitivity was determined, five resistant strains were found. The shortest period of PAS therapy resulting in drug resistance was 157 days.

[4] The determinations of sensitivity to PAS and streptomycin were performed at the State Bacteriology Laboratory, Stockholm, Sweden.

PAS in Extrapulmonary Tuberculosis

The results of PAS treatment in extrapulmonary tuberculosis at Solliden Sanatorium are reported in table 4.

In these cases PAS was given for three to fourteen months, usually four to six months; the longer periods being cases of miliary tuberculosis. The dosage of PAS was the same as in pulmonary tuberculosis, i.e., 12 to 18 Gm. per day divided in five to seven doses. Cases of tuberculous laryngitis, empyema, and enterocolitis are not included in the table.

TABLE 4

Results of Chemotherapy in Extrapulmonary Tuberculosis

	NUMBER OF CASES	CURED	MUCH IMPROVED	IMPROVED	DEAD	
Tuberculosis cutis						
Lupus faciei	3	3	—	—	—	
Tuberculides	1	1	—	—	—	Only PAS per os
Ulcus tub. cutis	1	1	—	—	—	
Tuberculosis peritonei	8	5	2*	—	1	5 cases only PAS
Tuberculosis peritonei et salpingitis tuberculosis	6	6	—	—	4 (ileus) —	3 cases combination with streptomycin
Salpingitis tuberculosis	1	1	—	—	—	
Otitis med. tuberculosis	4	3	—	1†	—	Only PAS per os
Parotitis tuberculosis	1	—	1	—	—	Combination treatment
Tuberculosis renis	7	1	—	6	—	Only PAS
Tuberculosis miliaris	4	3	—	—	1 69 years	PAS + streptomycin to all but one patient
Tuberculosis miliaris with meningitis tuberculosis	2	—	1‡	—	1	
Meningitis tuberculosis	4	—	—	—	4	

* Still treated

† A several-years-old tuberculous otitis.

‡ Two relapses of meningitis reacted to treatment. The miliary spread seems to be controlled.

In all cases of tuberculosis of the skin the diagnosis was confirmed by biopsy. All of the patients received only PAS orally, and the results were excellent (see table). These good results are in agreement with those reported by Lemming (17) (one case of tuberculous ulcer of the skin) and by Lightbound (18) (lupus cases).

The diagnosis of tuberculous otitis was confirmed by positive guinea pig test.

The patients with renal tuberculosis had a typical roentgenographic picture and positive guinea pig test (urine). The patient classified as cured (one kidney removed earlier for tuberculosis) showed a normal urogram, negative guinea

pig test, and a normal bladder by cystoscopy after PAS treatment. The last examination was six months after PAS therapy. Good preliminary results with PAS in renal tuberculosis have also been reported from Switzerland and Sweden (5, 7, 19).

The patients with miliary tuberculosis all had miliary nodules visible in the ocular fundi and cultures positive for *M. tuberculosis* on gastric lavage. The meningitis cases had positive guinea pig tests from the cerebrospinal fluid. Several reports of good results with streptomycin combined with PAS or sulfones have been published (3, 20, 21), but our experiences with the same therapy in tuberculous meningitis so far have been disappointing.

The effect of PAS in tuberculous enteritis has been described in an earlier publication (6). To date we have treated 36 patients with tuberculous enterocolitis (confirmed by typical roentgenographic picture) with PAS. Twenty-seven were completely cured, 8 considerably improved. The combination of PAS and a short course of streptomycin treatment gives more rapid results, especially if there is a tuberculous stricture of the intestine with danger of ileus. Since PAS increases peristalsis, gastrointestinal symptoms may be increased at the beginning of treatment.

Beneficial effect in a case of tuberculous salpingitis and peritonitis was demonstrated. The patient was admitted in an extremely poor condition after being treated conservatively for five months in another hospital.

Twenty-two patients with tuberculous empyema have been treated with PAS, most of them locally, as well as orally, with a 10 per cent solution of sodium-PAS. Results were as follows: 9 patients cured without any residua; 6 cured with a still open, but sterile, pleural space; one cured after thoracoplasty; and one is now ready for thoracoplasty after permanent suction drainage. One patient is dead. The remaining 4 patients, who refused surgical treatment, are still being treated with PAS but are now ambulant and in good condition.

These good results are in contrast to previous poor results in cases of tuberculous empyema (22). Similar favorable reports of PAS treatment of empyema have been published by others (23, 24), whereas trials with streptomycin in this disease have been generally disappointing (25).

Side effects of PAS are not encountered frequently, although nausea, burning epigastric pain, and diarrhea sometimes occur. These symptoms are reduced by giving the sodium salt of PAS or sodium bicarbonate with the acid. One of these patients developed fever and a skin rash and one patient developed fever with a slight, temporary granulocytopenia. No serious reactions to PAS have been observed among our patients.

SUMMARY

The results of treatment with PAS in more than 300 patients with pulmonary and extrapulmonary tuberculosis are reported. PAS is a valuable drug, though in pulmonary tuberculosis it is slightly less effective than streptomycin. Bacterial resistance to PAS does occur, in the earliest case in this study after 184 days of treatment. In combination with streptomycin, bacterial resistance to streptomycin and possibly also to PAS seems to be delayed or prevented.

Tuberculous empyema and enterocolitis are favorably influenced by PAS, and in various other kinds of extrapulmonary tuberculosis it has been very effective, particularly in mucous membrane and skin tuberculosis.

Toxic reactions to PAS are seldom seen and usually consist of mild nausea, heartburn, and diarrhea.

SUMARIO

El Acido Para-Aminosalicílico (PAS) en la Tuberculosis Pulmonary Extrapulmonar

Preséntase aqui el resultado del tratamiento con el PAS en más de 300 enfermos con tuberculosis pulmonar o extrapulmonar. El PAS es una droga valiosa, si bien en la tuberculosis pulmonar ligeramente menos eficaz que la estreptomicina. No deja de presentarse resistencia al PAS, sucediendo esto en el caso en que apareció más tempranamente en esta serie al cabo de 184 dias de tratamiento. Cuando se combina con la estreptomicina, parece demorarse o impedirse la farmacorresistencia a la última y posiblemente también al PAS.

El empiema y la enterocolitis tuberculosos son afectados favorablemente por el PAS, el cual se ha mostrado muy eficaz en otras varias formas de tuberculosis extrapulmonar, y en particular en la tuberculosis de las mucosas y la piel.

Las reacciones tóxicas al PAS son raras, consistiendo por lo general en leves náuseas, pirosis y diarrea.

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PARA-AMINOSALICYLIC ACID THERAPY IN INTESTINAL TUBERCULOSIS[1,2]

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INTRODUCTION

Para-aminosalicylic acid (PAS) is the substance which J. Lehmann (1, 2) after trial of a number of benzoic and salicylic acid derivatives, considered worthy to be tried clinically because of its strong bacteriostatic effect on the tubercle bacillus and its low toxicity in animal experiments. In cooperation with G. Vallentin (3), a beginning was made in 1944, and PAS has shown itself to be a valuable adjunct in tuberculosis therapy. During 1948 a comprehensive investigation of the clinical effects of PAS was carried out in Sweden and compared with control cases. Under these conditions a statistically verified therapeutic effect of the drug was demonstrated (4).

Early in the studies of PAS it was found that the most marked effects appeared in cases of intestinal tuberculosis. In 1948 Carstensen and Sjölin (5) gave an account of 22 cases of PAS-treated intestinal tuberculosis, of which 21 were verified by roentgenogram, and one, post mortem. In 19 cases, the clinical symptoms of intestinal involvement disappeared after 2 to 4 weeks of treatment, and a lasting general improvement was obtained. In 3 cases, the intestinal condition improved, although the general condition deteriorated with a fatal termination in one case. Eleven cases were examined roentgenographically after treatment and improvement was shown in 5 of these, which in 2 instances could be classified as complete regression of the lesions. With the exception of this investigation, only occasional cases have been published (6, 7, 8).

Good results have also been obtained in the treatment of intestinal tuberculosis with streptomycin, with very rapid regression of the clinical symptoms. The drug was administered parenterally or orally, and in enemata (9, 10, 11). Good results have also been reported from Germany following the use of the thiosemicarbazone TB 1/698E (12, 13, 14).

The frequency of intestinal tuberculosis in Sweden is not known with certainty, for this complication of pulmonary tuberculosis, as elsewhere, has not been systematically diagnosed in the past because of the earlier lack of specific therapy. In 1938 Tisell (15) published an investigation from this hospital on the diagnosis of intestinal tuberculosis. This work comprised 178 cases, of which 45 per cent were roentgenographically positive for intestinal tuberculosis. The material was selected from cases of advanced pulmonary disease, however, and is as little significant of the actual frequency of intestinal tuberculosis as are the large statistics of post-mortem material with a frequency for intestinal tuberculosis vary-

[1] From Söderby Hospital, Uttran, Sweden.

[2] This investigation has been carried out with the help of a grant from the Swedish National Association against Tuberculosis.

ing from 40 to 90 per cent (17, 18). According to Tisell, in the investigations of American writers with larger collections of statistics, the frequency of intestinal complications in cases of minimal pulmonary tuberculosis varies between 1.0 and 1.6 per cent, and in far advanced lung disease, between 18.1 and 25.7 per cent.

MATERIAL AND METHODS

The following investigation comprises 22 cases of secondary intestinal tuberculosis treated with PAS at Söderby Hospital, beginning in 1948. In these patients, the colon had been examined roentgenographically because of clinical symptoms which could not be explained by the already diagnosed pathologic changes, notably in the lungs. On the other hand, roentgenographic examination of the colon had not been carried out as a routine on all admitted cases. Only those cases have been included in which a roentgenogram typical for intestinal tuberculosis has been found before the commencement[1] of treatment.

The examinations (barium enema and contrast meal) have, with few exceptions, been carried out at this hospital, most of them by the writer.[2] Other cases with a clinical picture suggestive of intestinal tuberculosis, which were successfully treated with PAS but where intestinal lesions have not been roentgenographically demonstrated, have not been included. Among others, Tisell (15) and Hertzberg (16) have pointed out that the roentgenographic findings are of decisive importance in the diagnosis of intestinal tuberculosis, as this complication often runs a symptom-free or almost symptom-free course. On the other hand, pulmonary tuberculosis without intestinal tuberculosis often gives rise to the same symptoms as are present in intestinal disease, e. g., gastric distress and abdominal pain.

The investigation shows that PAS has such an excellent therapeutic effect on intestinal tuberculosis that the prognosis of the case would appear to be largely dependent on the outcome of the initial disease, pulmonary tuberculosis. As a consequence, the cases are divided into the following five groups.

1. Cases with pulmonary regression without collapse therapy
2. Cases with successful pneumothorax
3. Cases with unsuccessful pneumothorax
4. Thoracoplasty cases
5. Cases unsuitable for collapse therapy

Dosage, Method of Administration, and Side Effects of PAS

In these cases, PAS has been given orally in the form of coated granulate[3] in a quantity of 14 Gm. per day, divided into four doses of 5, 2, 2, and 5 Gm., respectively, administered with meals. As PAS granulate contains 70 per cent para aminosalicylic acid, 14 Gm. of the granulate are equivalent to 9.8 Gm. of PAS. With this dosage a blood concentration of 2 to 8 mg. per 100 cc. is reached. Short interruptions in therapy have occasionally been necessary because of lack of access to the drug and, less often, because of side effects. For various reasons the period of treatment has been short in Cases 10, 12, and 21. The period of treat-

[1] Valuable help in the examination of roentgenograms has been received from Dr. K. Lindblom, Lecturer in Radiology and Docent of the Karolinska Institute, Stockholm.

[2] PAS granulate used in this investigation is manufactured by Ferrosan Ltd., Sweden.

ment was intended to be three months, but this time has often been lengthened with regard to the lung process and often in preparation for collapse therapy.

Side effects: The toxic reactions caused by PAS are, in general, very mild and no lasting injurious effect has been observed. In the material of this investigation, 16 patients have had more or less frequent loose stools during PAS therapy. Of these patients, 12 had loose stools and 3 had alternating constipation and diarrhea before the introduction of PAS therapy. With the exception of some intial pain in one case, the loose stools during treatment have not been associated with pain, and, as a rule, have been easily controlled with tincture of opium. Additional discomforts have been nausea and vomiting for the first two weeks in 5 cases, and "heartburn" in 3 cases. These symptoms have been treated with antacids. In no instance has it been necessary to discontinue PAS for more than about a week because of side effects.

Roentgenographic Examination

Contrast examination of the intestine has been carried out chiefly by barium enema, which is well suited for studying the elasticity of the colon under fluoroscopy and the occurrence of changes which are present throughout the examination. The terminal ileum has, in this way, been accessible for examination in most cases. Goldberg, Sweany, and Brown (18) and others have shown that intestinal tuberculosis nearly always begins in the ileocecal region which, by means of barium enema, is easily accessible for thorough examination. Contrast meal has been given in addition in one-half of the cases. Analagous with Forsell's observations of duodenal ulcer, Tisell has shown that mucous membrane ulcerations in the colon are surrounded by high protecting folds, by means of which, on a roentgenogram, niches may be seen emanating from the intestinal lumen. As their communications with the intestine sometimes could not be contrast-filled, isolated flecks of contrast arise; these are designated "islands of contrast." Often no ulcerations are seen but they are judged to be present by the neuromuscular reaction, with high swollen folds of mucous membrane, niches, islands of contrast, obliterated haustration, and a lumen narrowed by contraction. The narrowing is often of such a degree that the lumen can only with difficulty be filled out as a thin string. Where there are deeper lesions in the intestinal wall, with involvement of the muscle proper and loss of its contractile power, conditions are present for an irreversible stenosing process.

RESULTS

With regard to roentgenographic findings the cases can be divided into 2 groups: (*1*) cases of ulcerative or pre-ulcerative lesions, with or without reversible contractures (the majority); (*2*) cases of irreversible stenosis and ulcerative lesions, e. g., Cases 4, 8, 20, and 22.

Of the first group, there was complete roentgenographic regression in 10 cases. The observation period in these cases extended from the commencement of PAS therapy to the last negative roentgenogram, a range of 6 to 16 months with an average of 11½ months. Almost complete regression was observed in Case 9, and considerable regression in 3 (Cases 1, 12, and 19). Of these last, Case 12 was treated for only 6 weeks. Of the remainder in this group, 3 patients died of far advanced pulmonary tuberculosis (as also did one of the patients with considerable regression, Case 19), 1½, 8, 15, and 16½ months, respectively, after the beginning of PAS therapy. One patient has not presented himself for follow-up roentgenograpic studies, but is subjectively symptom free.

In the other group, 2 patients (Cases 8 and 22) had a cone-shaped deformity of the cecum and ascending colon, with ulcerative lesions which underwent re-

gression in one instance. Follow-up roentgenographic studies were not carried out in Case 22, but autopsy showed ulcerative lesions. The remaining 2 (Cases 4 and 20) are of much greater interest. In both, signs of the marked ulcerative lesions disappeared under treatment (figures 1 and 2). Stenosis remained. In Case 20, roentgenographically verified intestinal tuberculosis was present 15 months be-

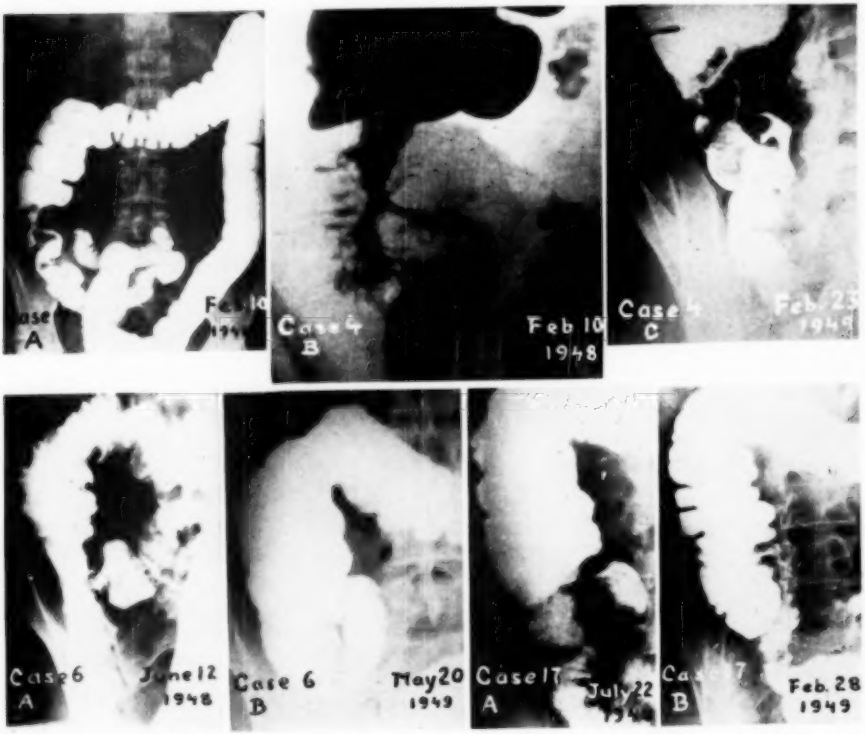

FIG. 1. Cases 4, 6, and 17

Case 4 (A and B). Stenosing process with ulcerations. The latter have disappeared during PAS therapy (C).

Case 6 (A and B). Ulcerative process treated by PAS with very good effect.

Case 17 (A and B). Complete regression of ulcerative tuberculosis in cecum and ascending colon.

fore PAS therapy was begun (figure 2). In all 18 cases which were examined by roentgenogram after treatment, there was evidence of regression of the lesions.

Temperature: From whatever point of view one regards the material, the effects of treatment have been very good. A fall in temperature has been observed in most cases starting from the first days of therapy. Before PAS treatment, all

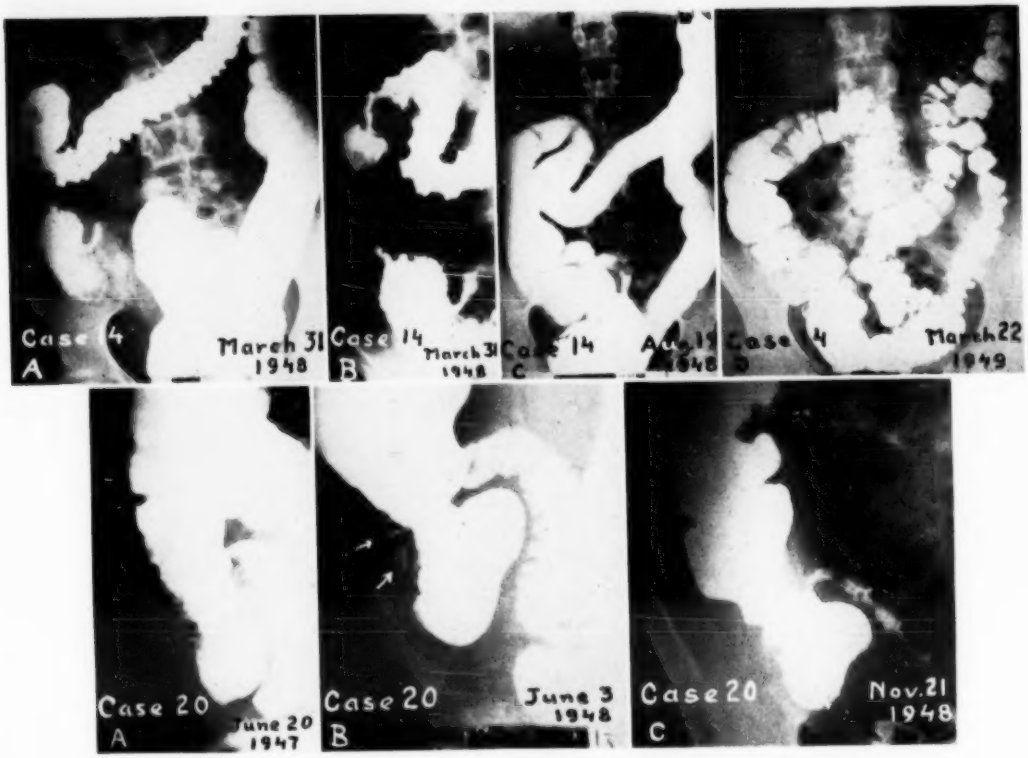

FIG. 2. Cases 14 and 20

Case 14 (A and B). Ulcerative process with extreme narrowing of lumen. After PAS, regression (C); normal roentgenogram (D).

Case 20 (A). Tuberculous process in cecum and ascending colon 12 months before PAS.

(B). Stenosis and deep ulcerations.

(C). No ulcerations after PAS.

patients except one (Case 20) were febrile; 13 were afebrile after one month of treatment, 16 after 2 months, and 18 after 3 months. In figure 5 is shown the average temperature of all cases for 4 months, including one month before PAS therapy. The immediate temperature-reducing effect of PAS is easily seen. Only in one case, with the exception of the surgical cases, has the temperature, after an initial decrease, risen under treatment (Case 11). Together with the striking improvement in the general condition of almost all of the patients, the weight

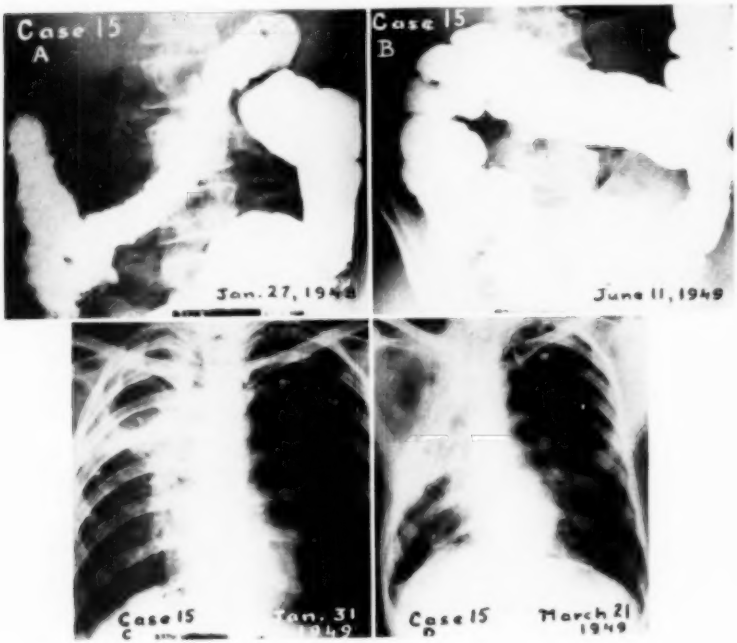

FIG. 3. Case 15

(A). Extensive ulcerative intestinal tuberculosis.
(B). Complete healing after PAS.
(C). Huge cavity right upper lobe. (Jan. 31, 1948) (Not 1949)
(D). After thoracoplasty.

has increased in all but 2. In some cases, the gain in weight has been very great, particularly when the patient has been cachectic. In such cases, the treatment has certainly been life saving. Since the discontinuation of PAS therapy, many patients have gained further in weight.

Erythrocyte sedimentation rate (ESR): Of the laboratory investigations, special importance has been attached to the erythrocyte sedimentation rate, the percentage of nonfilamented neutrophils, and the concentration of hemoglobin. The

ESR has most often, after a long period of elevation, fallen in immediate association with PAS therapy. In the cases where an increase has occurred, it has been reasonably explained by the status of the pulmonary lesion or by the performance of surgery. When the treatment has been of three months' duration or longer,

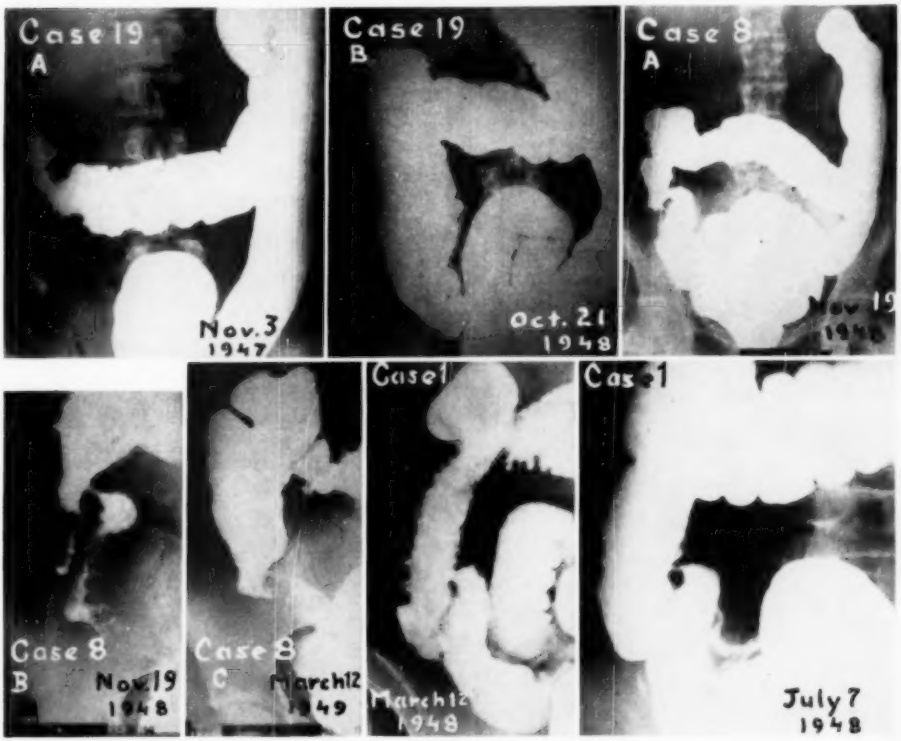

FIG. 4. Cases 19, 8, and 1

Case 19 (A). Extreme narrowing of cecum, ascending colon, and proximal transverse colon.

(B). After PAS; good dilatation.

Case 8 (A and B). Cone-shaped deformity of cecum with ulcerations.

(C). Stenosis remains; no islands of contrast or niches after PAS.

Case 1 (Left). Severe ulcerative process.

(Right) Marked regression after PAS.

in nearly all cases the nonfilamented neutrophils have decreased from a very high percentage to normal values. The average increase of hemoglobin was from 78 to 86 per cent. In figure 6 has been listed the average values for all cases of the percentage of nonfilamented neutrophils, weight, ESR, and hemoglobin for 4 weeks

before and 21 weeks after the commencement of therapy. It should be observed that the chart represents only patients in hospital whose numbers successively decrease. After 21 weeks the total number was 17. Four patients were discharged from hospital, and one had died.

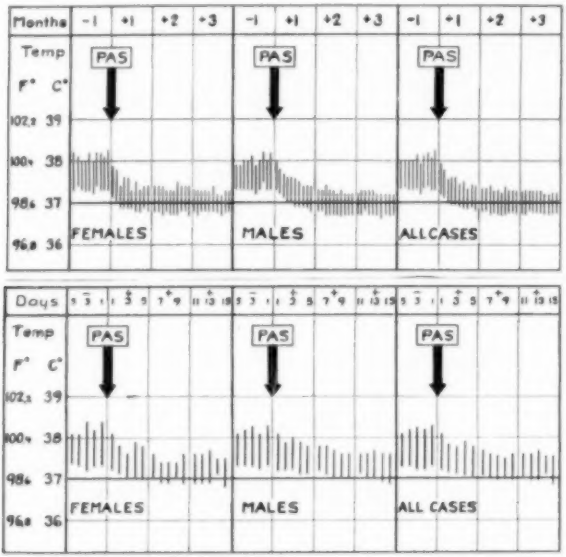

Fig. 5. Average temperature for all 22 cases. In the upper curve, each line represents the average for 3 days. In the lower, the temperature is recorded daily.

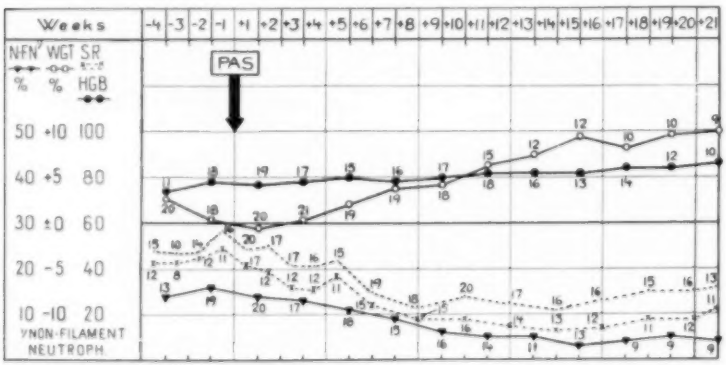

Fig. 6. Average for all 22 cases of weight, sedimentation rate, hemoglobin, and nonfilament neutrophils. Fatal cases are excluded from the lower sedimentation rate curve. The figures by the curves give the number of cases included in each average.

Symptoms: Of the 18 patients who had abdominal pain before PAS treatment, most were relieved during the first weeks, and the pain disappeared entirely or became insignificant after 1 to 8 weeks of treatment. All patients, with one exception (Case 11), had normal stools after the cessation of PAS. To complete the account of subjective symptoms experienced before, during, and after PAS therapy, the 18 patients who were alive in June 1949 have filled out a questionnaire. The answers show that at this time 13 patients were symptom free, 3 had occasional slight epigastric pain although they showed complete roentgenographic regression (Cases 2, 5, 13), and one (Case 4) had some meteorism and discomfort after meals. Although she was pregnant at that time, her intestinal stenosis could have given rise to the abdominal symptoms. One patient (Case 19) again had diarrhea without abdominal pain, in association with increased activity of the pulmonary lesion after freedom from symptoms for one year.

Case 2 has been included in this series, as roentgenographically positive intestinal lesions were present 5 months before PAS therapy was commenced. Although no characteristic roentgenographic signs remained when chemotherapy was begun, he still had extremely severe subjective distress which was decisively improved by PAS.

Post-mortem findings: Of the 5 fatal cases, autopsy has been carried out on 3 patients. All showed ulcerative intestinal lesions. Histologic examination in one patient (Case 21) showed signs of recent lesions and of lesions in a state of healing, of a type which can appear without chemotherapy. In another patient (Case 19), an extensive mucous membrane defect was replaced by granulation tissue rich in connective cells in which a few recent lesions were present.

Pulmonary lesions: Of the 22 patients, 13 had no collapse therapy during the period of PAS treatment. In 7 of these patients regression of the pulmonary lesions in immediate association with PAS therapy occurred, an improvement which was considerable in 2 patients (Cases 4 and 17). In 5 cases the chest roentgenogram was unchanged and in one (Case 21) there was progression of disease during the very short period of PAS therapy (23 days). In the 9 cases which had simultaneous collapse therapy, no progression of pulmonary disease occurred. In 3 of the 4 patients in group 1 for whom collapse therapy had earlier been considered, pulmonary regression was so considerable after PAS that collapse therapy was no longer considered to be indicated. Seven patients were sufficiently improved so that thoracoplasty could be performed. Of these, 2 have already completed operation, 2 are now undergoing the procedure, and one is ready for operation. In all of these patients, thoracoplasty would have been unthinkable without preoperative chemotherapy. The remaining 2 patients (Cases 18 and 19) declined thoracoplasty and died later of hemoptysis. In association with progression of the pulmonary disease, a total of 5 patients have died after the completion of PAS therapy. The period between cessation of therapy and death was: two weeks for one patient, two months for 2 patients, and eleven months for the remaining 2 patients. One of these patients died of acute monocytic leukemia, but any connection of this condition with PAS therapy is considered to be most unlikely.

In the cases where there has been therapeutic control of the lung disease

(groups 1, 2, and 4), there have been no deaths and no progression of the intestinal lesions. In the other groups, all deaths have occurred in association with progression of the pulmonary disease.

Bacteriologic findings: The sputum from 14 patients was positive for *M. tuberculosis* before PAS treatment. After one month, this figure fell to 8, and after two months to 3, only to rise after six months to 7. These were patients with pulmonary cavitation and illustrate the experience obtained from other PAS-treated patients that, in the presence of cavitation, *M. tuberculosis* often disappears from the sputum during PAS therapy only to reappear later.

Case 7. I. K., a 27-year-old female, was admitted to this hospital on June 21, 1948 (parturition, April 24, 1948). A chest roentgenogram, June 15, 1948, showed a process in the left upper lobe with cavity and moderate parenchymatous opacities in the right upper lobe. Left pneumothorax was induced July 6, 1948 and satisfactory collapse was obtained after two adhesion sections. Before admission, no abdominal symptoms were present, but subsequently frequently cramping abdominal pain after meals was present. As the temperature rose, although treatment of the pulmonary disease was free from complications, roentgenographic examination of the colon was made on November 23, 1948. A very irregular, finely serrated mucous membrane contour was seen, chiefly in the ascending colon with haustration largely lost in the proximal part of the colon. PAS was commenced on the same day, and was followed by an immediate effect on the temperature and a very rapid effect on the sedimentation rate and nonfilamented neutrophils. The abdominal discomfort disappeared after one week, but for the first two weeks there was slight nausea, sometimes with vomiting, and one loose stool daily. From December 22 to 24, 1948, pain was present in the right lower abdomen and a rise in temperature occurred. The consulting surgeon suggested the presence of tuberculous abdominal adenitis, and no laparotomy was performed. Acid regurgitation and "heartburn" under continued PAS therapy were treated with antacids. The patient has been symptom free since the discontinuation of PAS, and has an excellent appetite. *Barium enema* and *contrast meal* in March 1949 show a completely normal colon. The relatively lengthy PAS treatment, 5¾ months, was largely motivated by the lesion in the right lung which, because of an earlier postpneumonic empyema, could not be treated with pneumothorax. This lesion has undergone considerable regression.

Case 14 (figures 2 and 7). E. M., an 18-year-old female, was found to have minor lesions in both upper lobes in 1943. In 1945 to 1946 there was progression of the disease with cavity formation in the left upper lobe. The patient was admitted to Söderby Hospital in August 1946, and attempts to establish pneumothorax on both sides were unsuccessful. Together with bilateral progress of disease and periodic intestinal discomfort, a protracted deterioration began in September 1947, with intermittently high temperature which rose further in March 1948. At this time, the intestinal symptoms increased, with frequent diarrhea and right-sided abdominal pain. *Contrast studies* of the colon in March 1948 showed extensive ulcerative lesions of the mucous membrane in the cecum and ascending colon which could be filled only with difficulty in places as a thin string, and a very irregular mucous membrane in the transverse colon. After treatment with Sulftalyl (Ftalylsulfanilamidotiazol) for two months, there was a brief improvement of the intestinal symptoms but the general condition deteriorated quickly, the temperature became high, and she became cachectic. Because of her extremely ill general condition, she could not be weighed, but on June 7, 1948 her weight was 37.5 Kg. PAS therapy was administered for three months, starting on May 12, 1948. The effect on the temperature, ESR, and nonfilamented neutrophils is seen in figure 7. Before treatment, the patient was having two to three foul-smelling stools each day. With PAS, the foul smell disappeared but the number of stools increased; this was easily controlled by tincture of opium. Gradually the bowel movements became more

formed, and from the second day after the cessation of PAS she had one formed stool per day. The abdominal pain quickly decreased and disappeared after six to eight weeks. Her weight increased by 9.3 Kg. in six months. *Barium enema* and *contrast meal* in August 1948 showed a considerable improvement, with slightly irregular mucous membrane relief and a

TABLE 1

Results of PAS Therapy in Secondary Intestinal Tuberculosis

NUMBER	NAME	AGE AND SEX	DURATION			SEDIMENTATION RATE (WESTERGREN)		NONFILAMENTED NEUTROPHILS		HEMOGLOBIN		WEIGHT‡				
			PAS therapy	Observation time		Before PAS	After PAS	Before PAS	After PAS	Before PAS	After PAS	Before PAS	After PAS	Gain or loss	Last recorded weight in 6 months observation period	Gain or loss
				1*	2†											
			mos.	mos.	mos.					*per cent*	*per cent*			*per cent*		*per cent*
1	B. F.	M., 19	3½	3	15	27	2	13	2	80	92	57.3	58.8	+2.7	58.8	+2.7
2	K. F.	M., 34	5	9½	15	53	2	23	2	70	91	47.2	50.2	+6.4	50.5	+7.0
3	Å. P.	M., 22	3	13½	15½	94	2	22	6	67	94	62.8	71.8	+14.3	74.5	+18.6
4	A. T.	F., 34	5½	12	15½	53	10	7	9	84	80	68.0	76.0	+11.7	76.0	+11.7
5	K. E.	F., 20	3	7	11	48	8	17	4	79	81	45.7	50.5	+10.5	49.5	+8.3
6	G. F.	F., 29	3	10	12½	55	12	8	7	67	93	44.5	53.5	+20.2	53.5	+20.2
7	I. K.	F., 27	5¾	6	8	41	5	7	0	82	87	51.9	55.8	+7.5	55.9	+7.7
8	K. O.	F., 24	6	6	8	57	25	12	9	82	72	52.3	52.1	−0.4	52.1	−0.4
9	A. C.	F., 25	6	9	9	34	20	20	4	80	81	40.6	48.0	+18.2	48.0	+18.2
10	B. L.	M., 19	1¾	—	14½	57	62	9	6	85	86	54.3	56.1	+3.3	56.1	+3.3
11	A. L.	F., 36	4½	—	8	74	118	8	9	62	55	40.0	42.8	+7.0	43.0	+7.5
12	F. S.	M., 30	1¾	14½	15	63	79	30	12	89	83	57.6	59.0	+2.4	59.0	+2.4
13	E. E.	M., 39	3	15	16	46	14	15	5	75	76	63.0	63.3	+0.5	63.3	+0.5
14	E. M.	F., 18	3	10	12½	51	40	28	12	76	83	40.0	41.5	+3.7	44.0	+10.0
15	N. N.	M., 30	7	16	16	57	19	8	4	77	90	52.4	55.0	+5.0	55.0	+5.0
16	K. R.	M., 25	5	14	16	13	12	9	4	88	90	66.6	66.4	−0.3	66.4	−0.3
17	J. W.	M., 32	9	10½	12	38	17	5	4	84	99	65.0	72.2	+11.1	72.2	+11.1
18	K. B.	M., 29	4¼	4½	15	89	47	12	2	74	77	57.2	59.3	+3.7	59.5	+4.0
19	M. E.	F., 32	4	9	16½	118	41	16	3	58	76	41.7	52.5	+25.9	54.8	+31.4
20	J. H.	M., 29	3½	13½	14	18	13	8	6	88	94	64.3	66.0	+2.6	65.4	+1.7
21	J. N.	M., 56	¾	—	1½	64	20	25	23	53	60	51.3	51.4	+0.2	51.4	+0.2
22	S. Ö.	M., 29	3¼	—	5	29	50	28	13	98	83	53.7	56.8	+5.8	52.6	−0.2

* Observation time 1 covers the period from the commencement of PAS therapy to the last intestinal roentgenogram.

† Observation time 2 covers the period from the commencement of PAS therapy to the last contact with the patient (until August 1, 1949).

‡ Weight is calculated as a percentage of gain or loss of the weight at the *commencement* of PAS therapy.

fairly well-pronounced haustration. *Contrast enema* in March 1949 showed a completely normal picture. The patient has been completely free from abdominal symptoms after PAS therapy. The lesions visible on the chest roentgenogram have shown some stabilization, and the patient's good general condition has made it possible to prepare her for thoracoplasty.

TABLE 2

Intestinal and Pulmonary Roentgenograms Before and After PAS Therapy

CASE NUMBER AND NAME	SEX AND AGE	INTESTINAL STATUS BEFORE PAS THERAPY	PAS THERAPY	INTESTINAL STATUS DURING AND AFTER PAS THERAPY	PULMONARY STATUS AT THE COMMENCEMENT OF PAS THERAPY	PULMONARY STATUS AFTER PAS THERAPY	PULMONARY STATUS AT LAST FOLLOW-UP ROENTGENOGRAM	REMARKS
Group 1. Pulmonary regress without collapse therapy								
1 B. F.	M. 19	March 12, 1948. (B.E.): Cecum col. asc.: Ulc. process; lumen narrow; contr. islands and niche format; loss of haustration; term. il. dilated; ulc. changes in its walls (fig. 4)	April 5 to July 23, 1948	July 6, 1948. (B. E.): Smoother muc. mem. relief; still sl. irreg.; loss of haustration; less dilat. in term. il.; def. regress (fig. 4)	April 3, 1948: Bilateral apical lesions; small cavity R. apex	July 22, 1948: Regression; cavity lost to view	July 1, 1949: Unchanged	Discharged home
2 K. F.	M. 34	Sept. 25, 1947. (B. E.): Cecum: Muc. mem. coarsely irreg. as in int. tub.; similar changes in term. il. Feb. 22, 1948. (B. E.): Cecum, term. il.: Sl. irreg. but soft and changeable muc. mem. contour; not def. typical for int. tub.	March 3 to August 18, 1948	August 10, 1948. (B. E.): Normal rtg. December 22, 1948: (B. E.): Normal rtg.	March 4, 1948: Recent exudate L. base; small flecky lesions both upper lobes and L. base	August 19, 1948: Some regression of infiltration; no exudate	April 22, 1949: Unchanged since August 19, 1948	Discharged home
3 Å. P.	M. 22	March 19, 1948. (B. E.): Prox. col. asc.: Coarsely irreg. muc. mem.; loss of haustration; spast. in cecum. *Note:* Only in this case was PAS commenced before positive rtg.	February 20 to May 5, 1948	April 2, 1948. (C. M.): Unchanged since March 19, 1948. April 5, 1949: (B. E.): Comp. normal rtg.	February 17, 1948: Cloudy infiltration R. upper lobe and L. mid-field	May 4, 1948: Some regression	April 4, 1949: Almost complete regression	Discharged home
4 A. T.	F. 36	Feb. 10, 1948. (B. E.): Mkd. retr. of ileo-cecal region; pencil-wide lumen in cecum, prox. col. asc. and term. il., from which radiate contr. niches and islands. Prox. il. dilated (fig. 1)	February 13 to September 14, 1948	September 14, 1948. (B. E.): Contr. niches and islands lost to view; cecum has widened and presents smooth contours; otherwise, mkd. remaining stenosis. Feb. 23, 1949. (B. E.): Unchanged since Sept. 14, 1948 (fig. 1)	February 2, 1948: Widespread flecky lesions over entire R. lung and upper part of L. lung	October 19, 1948: Significant regression	May 30, 1949: Almost comp. regression	Discharged home Addendum. Since parturition, completely symptom free.

Group 2. Successful pneumothorax cases

5 K. E.	F. 20	Aug. 4, 1948. (B. E.) Aug. 26, 1948. (C. M.): Med. asp. col. asc.: Constant deformity and coarse, irreg. muc. mem. relief; loss of haustration	August 24 to November 26, 1948	Nov. 22, 1948. (C. M.): Normal rtg. Jan. 13, 1949. (B. E.): Normal rtg. Mar. 16, 1949. (B. E.): Normal rtg.	June 23, 1948: R. pneumothorax with good collapse.	December 15, 1948: Unchanged	June 2, 1949: Unchanged	Discharged to convalescent home
6 G. F.	F. 29	June 12, 1948. (B. E.): Cecum, col. asc. Irreg. swollen muc. mem. folds; scattered islands of contr.; almost comp. loss of haustration (fig. 1) June 28, 1948. (C. M.) July 2, 1948 (B. E.): Unchanged	July 13 to October 14, 1948	Oct. 13, 1948. (B. E.): Sl. irreg. muc. mem. relief; poor haustration, regression May 20, 1949. (B. E.): Normal haustration; muc. mem. normal. (Sl. irreg. contour in flex hepat. Pathological?) (fig. 1)	July 8, 1948: Satisfactory R. pneumothorax; slight inactive infiltration L. upper lobe.	October 6, 1948: Unchanged	July 14, 1949: Unchanged	Discharged home.
7 I. K.	F. 27	Nov. 23, 1948. (B. E.): Chiefly col. asc.: Finely serrated muc. mem. contour; haustration largely lost	November 23, 1948 to May 17, 1949	Mar. 8, 1949. (B. E.): Mar. 16, 1949 (C. M.): Regression. {Good haustration; muc. mem. sl. irreg. only in a few small places May 17, 1949 (B. E.): Normal rtg.	November 23, 1948: L. pneumothorax with good collapse; mod. parenchymatous opacities R. upper lobe	May 2, 1949: Unchanged	June 20, 1949: Some regress of R. infiltration	Discharged home
8 K. O.	F. 24	Nov. 19, 1948. (B. E.): Cecum, col. asc.: Cone-shaped deformity with fretted muc. mem. relief; a few niches and islands of contr.; term. il. narrowed at valv. Bauh. and dil. prox. (fig. 4)	November 23, 1948 to May 23, 1949	Mar. 12, 1949. (B. E.): Deformity almost unchanged; less contr. niches; contr. islands lost to view (fig. 4) May 18, 1949. (B. E.): Deformity remains, and must be regarded as irreversible; muc. mem. still irreg. but without contr. niches	November 18, 1948: Bilateral pneumothorax; exudative L. upper lobe lesions; small persistent cavity L. apex	May 23, 1949: Some bilateral regress, especially of the cavity in L. lung		Discharged to convalescent home

Group 3. Unsuccessful pneumothorax cases

9 A. C.	F. 25	Aug. 20, 1948. (B. E.): Cecum, col. asc.: def. narrowed, but vary somewhat in size during exam.; muc. mem. rather irreg., finely serrated; loss of haustration	August 28, 1948 to February 26, 1949	Feb. 24, 1949. (B. E.): Aff. parts have def. widened; muc. mem. only in places sl. irreg.; loss of haustration May 23, 1949. (B. E.): Aff. parts now of normal width. Haustration almost normal. Reg. muc. mem. picture.	August 5, 1948: Bilateral pneumothorax; persistent cavity on either side	February 23, 1949: One small cavity visible on either side. Regression	April 6, 1949: Unchanged since February 23, 1949	General condition good

TABLE 2—*Continued*

CASE NUMBER AND NAME	SEX AND AGE	INTESTINAL STATUS BEFORE PAS THERAPY	PAS THERAPY	INTESTINAL STATUS DURING AND AFTER PAS THERAPY	PULMONARY STATUS AT THE COMMENCEMENT OF PAS THERAPY	PULMONARY STATUS AFTER PAS THERAPY	PULMONARY STATUS AT LAST FOLLOW-UP ROENTGENOGRAM	REMARKS
			Group 3.—Continued					
10 N. L.	M. 19	April 29, 1948. (C. M.): Cecum, col. asc., most of col. transv.: Rigid, with jagged contours; loss of haustration; tenderness	May 10 to June 12, 1948	No further int. roentgenogram	May 3, 1948: L. sero-pneumothorax. Small R. apical infiltration	June 30, 1948: Unchanged	June 4, 1949: L. empyema pleurae. Otherwise unchanged since June 30, 1948	Discharged against advice after 6 weeks PAS therapy
11 A. L.	F. 36	January 21, 1948. (B. E.) January 23, 1948. (C. M.): Cecum, prox. col. asc.: Sl. irreg. muc. mem. relief. Haustration somewhat irreg.	January 29 to June 11, 1948	No further int. roentgenogram; post-mortem examination was refused	Jan. 26, 1948: Bilateral pneumothorax. Cavity L. apex. Not aff. by collapse	June 30, 1948: Unchanged	August 2, 1948: Progress	Died 8 months after the commencement of PAS therapy
12 *V.* S.	M. 30	April 28, 1948. (B. E.) May 4, 1948. (C. M.): Cecum, col. asc.: very irreg. muc. mem. relief; loss of haustration; spastic narrowing of int. lumen makes filling difficult	May 6 to June 18, 1948	July 19, 1949 (B. E.): Still irreg. muc. mem. relief; remaining but less mkd. spast. in cecum and col. asc. Regained haustration	Mar. 25, 1948: Bilateral pneumothorax. Cloudy opacities over most of L. lung and R. upper lobe	June 18, 1948: Unchanged	July 19, 1949: Progress; bilateral cavities; L. seropneumothorax	Uncooperative patient Addendum Died Oct. 1949. Autopsy: Healed and recent int. lesions
			Group 4. Thoracoplasty cases					
13 E. E.	M. 39	Mar. 22, 1948. (B. E.): Lat. col. asc.: very irreg. and coarse muc. mem. relief; irreg. muc. mem. relief also in term. il.	March 30 to July 1, 1948	April 4, 1949. (B. E.): Comp. regression July 8, 1949. (B. E.): Possibly sl. spast. in cecum; otherwise normal rtg.	March 30, 1948: Huge cavity L. upper lobe; satisfactory R. pneumothorax.	July 12, 1948: Unchanged	July 26, 1949: After first stage thoracoplasty, Jan. 13, 1949, and Monaldi drainage since Apr. 10, 1949, much smaller L. cavity	Addendum March 1950 Status quo

14 E. M.	F. 18	Mar. 31, 1948. (B. E.): Cecum, col. asc.: Mkd. narrowing to, in col. asc., the width of a thin string; muc. mem. very irreg.; comp. loss of haustration; col. trans.: very irreg. contour (fig. 2)	May 5 to August 12, 1948	Aug. 19, 1948. (B. E.) August 25, 1948. (C. M.): No spast.; Sl. irreg. muc. mem. relief; fairly good haustration (fig. 2) Mar. 22, 1949. (B. E.): Comp. normal rtg. (fig. 2)	April 14, 1948: Large cavities L. upper lobe; infiltration R. upper lobe	August 14, 1948: Unchanged	May 12, 1949: Cavities smaller; tendency to retr. L. lung	Ready for thoracoplasty Addendum Thoracoplasty March 1950
15 N. N.	M. 30	January 27, 1948. (B. E.): Cecum, col. to flex. lienalis: Coarse irreg. muc. mem. relief; islands of contr.; spasticity; loss of haustration (fig. 3)	February 2 to September 9, 1948	Nov. 1, 1948. (B. E.): Muc. mem. from lat. part of cecum sl. irreg.; otherwise normal rtg. June 11, 1949. (B. E.): Normal rtg. (fig. 3)	January 31, 1948: Huge cavity R. upper lobe; minor calcifications L. lung (fig. 3)	September 17, 1948: After thoracoplasty, cavity lost to view; L. lung unchanged	June 11, 1949: Unchanged since September 17, 1948; good collapse	Discharged home
16 K. R.	M. 25	February 26, 1948. (B. E.): Col. asc.: Mkd. contraction; muc. mem. very irreg.; loss of haustration; cecum could not be filled	March 19 to August 17, 1948	Aug. 14, 1948. (B. E.): Cecum, col. asc. now fill well; normal rtg. May 20, 1949 (B. E.): Normal rtg.	March 18, 1948: Ext. L. tub. with large upper lobe cavity; stationary R. infiltr.	August 12, 1948: Regression L. base	June 30, 1949: Good collapse after L. thoracoplasty.	Discharged home
17 J. W.	M. 32	July 13, 1948. (B. E.) July 22, 1948. (B. E.): Cecum, col. asc.: muc. mem. irreg. with coarse swollen folds; spast. of aff. parts. Loss of haustration (fig. 1)	July 21, 1948 to April 8, 1949	Feb. 28, 1949. (B. E.): Col. asc.; almost normal haustration; normal muc. mem.; cecum: spast. and sl. irreg. muc. mem. relief (fig. 1) May 23, 1949. (C. M.): Cecum fills well; normal rtg. June 9, 1949. (B. E.): Normal rtg.	June 28, 1948: Large cavity R. upper lobe; widespread flecky lesions L. lung field	April 26, 1949: Obvious bilateral regression	July 16, 1949: After thoracoplasty first stage July 13, 1949, partial R. collapse	Addendum Discharged home after completed thoracoplasty
Group 5. Cases unsuitable for collapse therapy								
18 K. B.	M. 29	January 9, 1948. (C. M.): Cecum, col. asc.: State of contraction with coarse irreg. muc. mem. relief; loss of haustration	January 23 to May 25, 1948	June 2, 1948. (B. E.) June 10, 1948. (C. M.): Aff. parts now easily filled; muc. mem. still irreg.; now of serrated type. No haustration.	January 19, 1948: Extensive L. tub.; cavity L. upper lobe. Widespread scattered infiltration R. lung	June 7, 1948; Obvious R. regression; L. lung unchanged	August 2, 1948: Unchanged since June 7, 1948	Refused thoracoplasty; disch. home against advice; died 15 months after the commencement of PAS therapy

TABLE 2—*Continued*

CASE NUMBER AND NAME	SEX AND AGE	INTESTINAL STATUS BEFORE PAS THERAPY	PAS THERAPY	INTESTINAL STATUS DURING AND AFTER PAS THERAPY	PULMONARY STATUS AT THE COMMENCEMENT OF PAS THERAPY	PULMONARY STATUS AFTER PAS THERAPY	PULMONARY STATUS AT LAST FOLLOW-UP ROENTGENOGRAM	REMARKS
				Group 5.—Continued				
19 M. E.	F. 32	November 3, 1947. (B. E.) November 7, 1947 (C. M.): Cecum, col. asc.: filled with difficulty only as a thin string; prox. trans. col.: Coarse irreg. muc. mem. relief; mkd. narrowing of lumen towards flex. hepat.; term. il. easily dilated (fig. 4)	January 25 to June 18, 1948	June 4, 1948 (B. E.) June 10, 1948. (C. M.): Cecum, col. asc.: quite easily filled; haustration indicated in distal col. asc.; muc. mem. finely serrated Oct. 21, 1948. (B. E.): Unchanged since June 10, 1948 (fig. 4)	January 11, 1948: Large cavity L. lower lobe; stationary R. apical lesions	June 10, 1948: Unchanged	May 4, 1949: Progression; bilateral cavities	Declined thoracoplasty; died 16½ months after commencement of PAS therapy. See autopsy report
20 J. H.	M. 29	March 8, 1947. (B. E.): Lat. part of cecum, prox. col. asc.: Coarse irreg. muc. mem. relief, with contraction on level of valv. Bauh. June 20, 1947. (B. E.): June 25, 1947 (C. M.): Unchanged (fig. 2) June 3, 1948. (C. M.): Constant rigid narrowing on level of valv. Bauh.; contr. niches and islands of contr. seen laterally in a semilunar defect (fig. 2); local tenderness	June 4 to September 20, 1948	September 21, 1948. (B. E.): No ulc. visible; int. lumen wider, but stricture remains (fig. 2) July 19, 1949. (B. E.): Constantly less semilunar defect lat. to valv. Bauh.	May 27, 1948: Status postpneumothorax bilateralis; retraction of R. lung; cloudy opacities L. upper lobe	Oct. 20, 1948: Unchanged	June 27, 1949: Cavity L. upper lobe	Disfunction of contralateral lung Addendum Thoracoplasty Feb. 1950; no int. symptoms
21 J. N.	M. 56	Sept. 20, 1948. (B. E.): Cecum, col. asc.: Irreg. muc. mem.; jagged contours; loss of haustration	September 21 to October 10, 1948	Nov. 25, 1948: (Autopsy: cecum, prox. col. asc. numerous small sores in the muc. mem.)	Sept. 21, 1948: Extensive bilateral old and recent lesions; L. apical cavity	No further lung roentgenogram (Autopsy: Extensive cavernous lung lesions.)		Died 6 weeks after commencement of PAS
22 S. Ö.	M. 29	March 1, 1948. (B. E.): Cone-shaped deformity of cecum and lower col. asc.; ulc. changes in term. il.; irreg. muc. mem.; numerous shallow niches.	March 10 to June 21, 1948	August 11, 1948: (Autopsy: Numerous small sores in the small intestine and cecum.)	March 8, 1948: Cavity L. upper lobe; status postpneumothorax bilateralis	July 14, 1948: Unchanged since March 8, 1948	August 2, 1948: Much progress L. lung and R. base	Died of acute monocytic leukemia 5 months after commencement of PAS therapy

Abbreviations

Aff.	= affected	dil.	= dilatation	retr.	= retraction
asc.	= ascending	format.	= formation	rtg.	= roentgenogram
B. E.	= barium enema	int.	= intestinal	term. il.	= terminal ileum
C. M.	= contrast meal	irreg.	= irregular	trans.	= transverse
col.	= colon	lat.	= lateral	tub.	= tuberculosis
comp.	= completely	mkd.	= marked	ule.	= ulcerative
contr.	= contrast	muc. mem.	= mucous membrane		
def.	= definite	reg.	= regular		

Case 18 (figure 3). N. N. was a 30-year-old male who received bilateral pneumothorax treatment between 1938 and 1942. In the beginning of 1947 relapse occurred with a large cavity in the right upper lobe. Unsuccessful attempts were made to re-establish pneumothorax. In the spring of 1947, loose stools and abdominal pain, localized to the right iliac fossa, appeared. The patient decreased in weight and was subfebrile. From October 1947 he showed obvious deterioration, with poor appetite and loss of weight. The bowel movements had become sluggish, and there was moderate intermittent lower abdominal pain. There was little change in the lung roentgenogram. The patient was admitted to Söderby Hospital on December 15, 1947. Roentgenographic studies of the colon on January 27, 1948 showed an extensive, ulcerative, intestinal tuberculosis with islands of contrast and loss of haustration, involving the colon from the cecum to the splenic flexure. PAS therapy was started on February 2, 1948. The stools became loose but not frequent during the first weeks, and were periodically so later. After one month he was free from abdominal discomfort. On Professor Crafoord's advice, thoracoplasty in three stages was performed. This was facilitated by

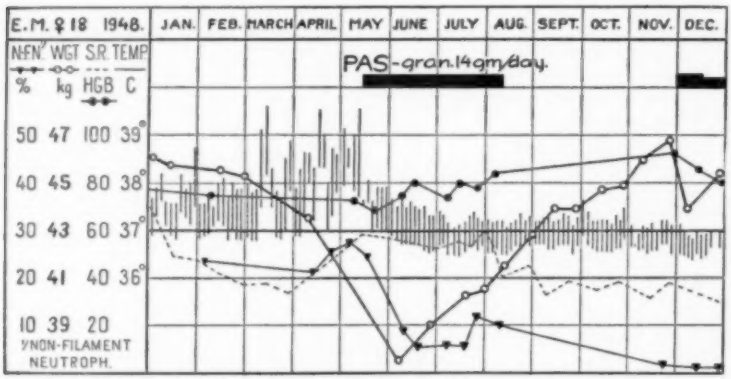
E.M. 8 18 1948.
JAN. FEB. MARCH APRIL MAY JUNE JULY AUG. SEPT. OCT. NOV. DEC.
SED. WGT S.R. TEMP
% kg HGB C
PAS-gran. 14 gm/day.
50 47 100 39°
40 45 80 38°
30 43 60 37°
20 41 40 36°
10 39 20
NON-FILAMENT NEUTROPH.

FIG. 7. Case 14. Extensive ulcerative intestinal tuberculosis with far advanced pulmonary tuberculosis, treated with PAS.

Monaldi cavity drainage. PAS therapy was well tolerated until the end of May when, because of nausea, a short interval in treatment was allowed. This indisposition was associated with signs of inflammation around the Monaldi drainage tube. Appendicectomy was performed on September 29, 1948. The appendix contained pus, its mucous membrane was gangrenous, and its walls were thickened. *A roentgenogram of the colon* on November 1, 1948 showed a normal picture with the exception of a small irregularity in the lateral part of the cecum. The patient was discharged to his home symptom free on November 8, 1948. Follow-up examination in June 1949 showed a normal intestinal roentgenogram and a good lung collapse without sign of cavity. He had increased further in weight, and felt well.

Case 19 (figure 4). M. E. was a 32-year-old female with bilateral pulmonary tuberculosis since 1936 and oleothorax on the left since 1939. She was admitted to Söderby Hospital in January 1947 with a recurrent cavity in the left lower lobe. For fully a year she was subfebrile, with shorter periods of higher temperature. In the summer of 1947, she began to have a period of diarrhea with abdominal pain. *Barium enema* and *contrast meal* were obtained in November 1947, but the flow of the enema became dammed up at the proximal end of the transverse colon, as the intestinal lumen was narrowed by gross irregular contours. Moreover, the ascending colon could only be filled out as a thin string with the help

of massage. The cecum could not be filled by *barium enema*, but was seen by *contrast meal* to be the size of a walnut. The terminal ileum dilated easily. At that time PAS was not available at this hospital. The patient's temperature rose further from December 1947, with many peaks of more than 39°C. Abdominal pain and diarrhea increased. The lung cavity increased in size and PAS therapy was commenced on January 25, 1948. She was then extremely ill, weighed only 41.7 Kg. compared with 57 Kg. in March 1947, and her condition was considered hopeless. The effect of PAS was very impressive. The temperature fell at once, and she was afebrile after two months. The former foul-smelling and frequent bowel movements changed to loose stools. Initial nausea and vomiting disappeared, as did the abdominal pain, in less than two months. She gained 12 Kg. in weight in 4½ months. *Opaque enema* and *contrast meal* in June 1948 showed considerable regression of the abnormalities. *Opaque enema* in October 1948 was unchanged. She was discharged to her home in October 1948 with unimproved pulmonary disease to await a possible thoracoplasty, which she later declined. For fully a year she reported herself as being free from intestinal symptoms. Increased activity in her disease in February 1949, with cavity in the right lung, was followed by hemoptyses and death on June 12, 1949. For the last six weeks of life she again had diarrhea but no pain. Her condition did not permit new roentgenographic studies of the colon. Because of the far advanced pulmonary tuberculosis, further PAS treatment was not considered to be justified.

Post-mortem examination (A. Bergstrand): The mucous membrane in the lower part of the small intestine was somewhat atrophic, smooth, and shiny, with occasional areas of hyperemia and hemorrhages. In a few places, small punched-out lesions were present. In the cecum and ascending and transverse colon, there was an extremely atrophic mucous membrane with hyperemia and small hemorrhages, and a small number of fresh tuberculous ulcerations, chiefly localized to the cecum and the boundary between the cecum and ascending colon. The lesions ceased distal to the splenic flexure, and the mucous membrane in the sigmoid colon was normal. The lymph nodes in the mesentery were somewhat enlarged and greyish-red. No necrosis or calcification was present. Bilateral apical cavities and widespread recent acino-nodose lesions were present in the lungs.

Microscopic examination (A. Bergstrand): Microscopic examination of the large intestine showed an almost complete loss of its mucous membrane. Only here and there were there insignificant remnants with a few gland ducts. In addition, the intestine's inner surface was covered with a granulation tissue rich in connective cells, the inmost layer of which was densely infiltrated with lymphocytes. In some places, recent ulcerations were present in this connective tissue, stretching out towards the muscle wall. These contained fibrin and polymorphonuclear leukocytes. Isolated patches of necrosis were also visible in the intestinal wall and were surrounded by a border of epithelioid cells. No Langhans' giant cells or granulation tissue typical for tuberculosis or *M. tuberculosis* could be observed. Nevertheless, although the granulations and fresh necroses did not present any typical appearance, this was, in all probability, a fresh tuberculous process. The small intestine showed no such changes as the colon, but on its serous surface there were one or two small patches of necrosis of more typical tuberculous appearance, with well-developed epithelioid cell membranes. Neither Langhans' giant cells nor *M. tuberculosis* could be demonstrated here. No amyloid was seen in the large or small intestine, although it was present in the liver, kidneys, and spleen.

Thus the examination showed a scar-like condition of healing in the whole colon up to and including the splenic flexure with a recent exacerbation in the form of scattered surface sores.

DISCUSSION

This investigation shows the excellent therapeutic effects of PAS in secondary intestinal tuberculosis. The conclusions are supported, as in previous studies, by very good clinical results, but also by corresponding and relatively rapid

roentgenographic regression of the intestinal abnormalities. The good effects of PAS in intestinal tuberculosis may depend on the good supply of blood and lymphatic vessels and on the high concentration of drug obtained in the intestine and intestinal wall by the oral administration of the drug.

What complete roentgenographic regression corresponds to, pathologically and anatomically, remains to be investigated. Histologic examination of the tissues of one patient with far advanced intestinal tuberculosis who had had one year's freedom from symptoms after therapy showed a healing process, with granulation tissue rich in connective cells in place of the almost destroyed mucous membrane.

It seems correct to assume that PAS interrupts an active intestinal process, even in advanced cases, thereby preventing the deleterious, often fatal, effects on the patient. It is important, however, to diagnose the cases early, in order to interrupt the process before irreversible changes with resulting stenosis take place.

Good results have been reported with other preparations, chiefly with streptomycin. This drug is associated with some toxicity, however, and drug-resistant tubercle bacilli emerge to predominance more rapidly than is the case with PAS. As a consequence, PAS seems to be preferable in the treatment of intestinal tuberculosis, as it is an almost always well-tolerated oral preparation, without hitherto observed lasting side effects. Moreover, clinically recognizable drug resistance has not yet been observed.[5] Then, too, it would appear to be wise to save the more rapid effect of streptomycin for the other nonintestinal, more serious complications which occur spontaneously or in association with operation. The important point to observe also is the risk of allergic reaction in personnel administering streptomycin, a risk which does not exist with PAS.

SUMMARY

1. Twenty-two cases of roentgenographically verified secondary intestinal tuberculosis treated with para-aminosalicylic acid (PAS) at Söderby Hospital are reported.

2. Complete roentgenographic intestinal regression was obtained in 10 cases, almost complete in one; there was considerable regression of the abnormalities in 7. In 4 cases there were no follow-up roentgenographic studies. Of these, one is subjectively symptom free and 3 are dead.

3. After a period of eight to sixteen months from the commencement of PAS therapy, 13 patients were entirely symptom free, 3 had mild abdominal discomfort, and one (now pregnant) had more pronounced symptoms. Five of the patients were dead.

4. In all 5 fatal cases, subjective improvement of abdominal symptoms after therapy had been observed. One patient died of acute monocytic leukemia which was not considered to be related in any way to the PAS therapy.

5. Of the 13 patients who, during the period of PAS treatment, were without

[5] Later experience shows that resistance may develop after 6 or more months' PAS therapy.

simultaneous collapse therapy, 7 had regression of pulmonary lesions; the status of the pulmonary lesion was unchanged in 5; and in one patient there was progression of the pulmonary disease. Thoracoplasty has been performed on 4 patients and another is ready for operation. Two others were prepared for thoracoplasty but declined the operation, and died later of hemoptysis.

SUMARIO

El Acido Para-Aminosalicílico en la Terapéutica Intestinal

1. Veintidós casos de tuberculosis intestinal secundaria, comprobada roentgenológicamente, fueron tratados con el ácido para-aminosalicílico en el Hospital Söderby.

2. En 10 casos, obtúvose, radiológicamente, completa regresión intestinal; en uno casi completa, y en 7 considerable. En 4, no hubo comprobación roentgenológica subsiguiente. De éstos, uno se halla subjetivamente asintomático, y 3 han muerto.

3. Al cabo de un período de ocho a dieciséis meses desde el comienzo de la para-aminosalicilicoterapia, 13 enfermos hállanse absolutamente asintomáticos, 3 tenían leve malestar abdominal y uno (mujer gestante) tenía síntomas más pronunciados; 5 habían fallecido.

4. En todos los 5 casos letales, hubo mejoría subjetiva de los síntomas abdominales después de la terapéutica. Un enfermo murió de leucemia monocitaria aguda, considerándose excluída la posibilidad de una relación etiológica con la PAS-terapia.

5. De los 13 enfermos, que durante el período de PAS-terapia no recibieron simultáneamente la colapsoterapia, 7 mostraron regresión pulmonar; el estado del pulmón no varió en 5; en uno hubo agravación. La toracoplastia ha sido ejecutada en 4 enfermos y otro se halla dispuesto para la operación. Dos pacientes más fueron preparados para la toracoplastia, pero rehusaron la intervención, y murieron más tarde de hemoptisis.

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FEBRILE REACTIONS TO PARA-AMINOSALICYLIC ACID[1]

JULIA R. DAVIN AND ARTHUR E. T. ROGERS

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The rapidly increasing utilization of para-aminosalicylic acid (PAS) as an adjunct to the treatment of tuberculous disease is based upon: (*1*) its inherent bacteriostatic action on *M. tuberculosis;* (*2*) its additive effect when administered simultaneously with streptomycin or dihydrostreptomycin; (*3*) its presumed ability to delay the emergence of streptomycin-resistant organisms during treatment with that antibiotic; and (*4*) its continued value in the presence of streptomycin-resistant tubercle bacilli. Unlike streptomycin, PAS is a therapeutic agent which need not be withheld because of its possible later importance for coverage of anticipated surgical situations, or because of the occurrence of irreversible toxic reactions following long continued periods of therapy. It is obvious, therefore, that the clinical application of PAS is justified in a large segment of all tuberculosis cases and that any toxic reactions which are observed should be given early recognition. It is the purpose of this report to call attention to a type of febrile reaction which, to our knowledge, has not been observed hitherto.

PAS has been used in this institution for a period of six months, and a total of 85 patients have been treated with it. Dosage has varied from 12 to 20 Gm. daily depending upon tolerance, the preparation used being an effervescent mixture of the drug with sodium bicarbonate and powdered sugar. As has been noted in the current literature, the chief deterrent to long-term administration of PAS has been the development of nausea, vomiting, and diarrhea. Less common complications are areas of pruritic dermatitis and occasional instances of bone marrow depression, evidenced by leukopenia with neutropenia. All of these reactions have disappeared quite promptly after discontinuance of the drug and in some instances subsequent readministration has been possible. However, 4 of our patients have developed an acute, severe, febrile reaction associated with malaise, vomiting, and prostration. This has occurred twice in patients receiving only PAS and twice in patients receiving both PAS and streptomycin. In one of the latter cases, the syndrome was duplicated after both drugs had been discontinued and PAS alone restarted. Since in all of these patients extensive pulmonary tuberculosis was present, the acute febrile episode was first believed to indicate the development of some tuberculous complication, such as pleural effusion, acute bronchogenic or hematogenous spread, or meningitis. Study of the patients, however, showed no evidence of such complications and withdrawal of the PAS resulted in dramatic defervescence with more gradual symptomatic improvement. The following are abbreviated protocols of the 4 cases.

CASE REPORTS

Case 1. L. V., a 35-year-old man, had far advanced pulmonary tuberculosis with an old right thoracoplasty and more recent contralateral disease. PAS was started with a daily dosage

[1] From the Los Angeles Sanatorium, Duarte, California.

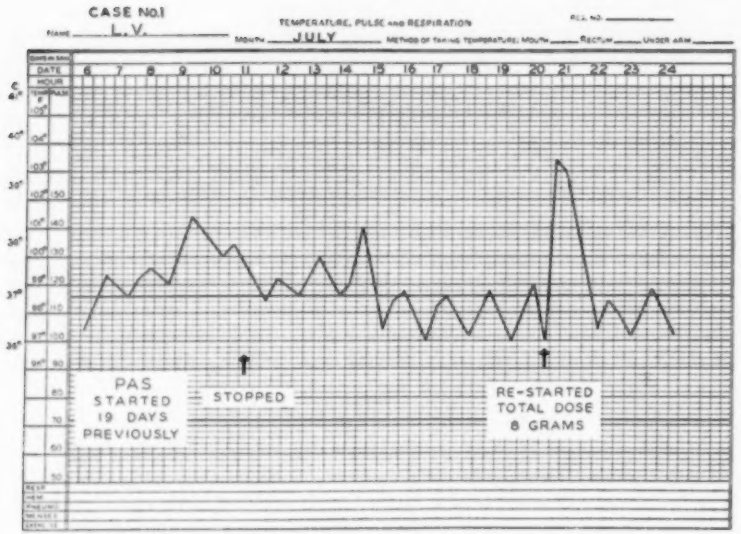

FIG. 1. Case 1 (L.V.) Temperature, pulse, and respiration chart

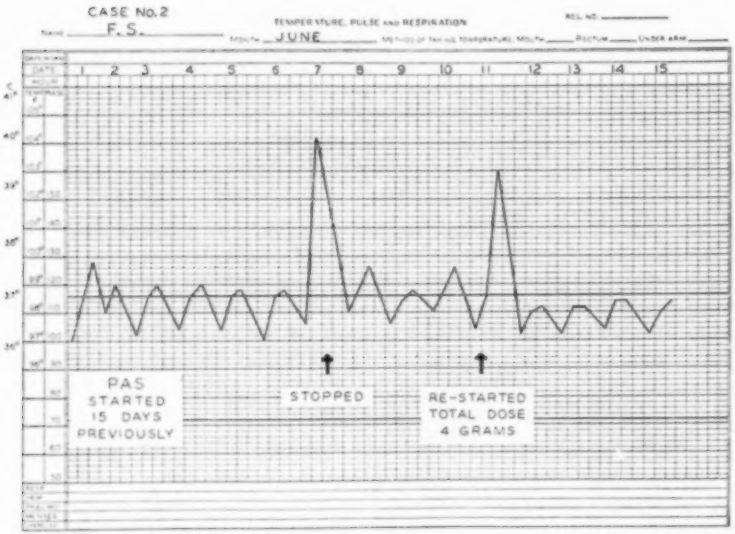

FIG. 2. Case 2 (F.S.) Temperature, pulse, and respiration chart

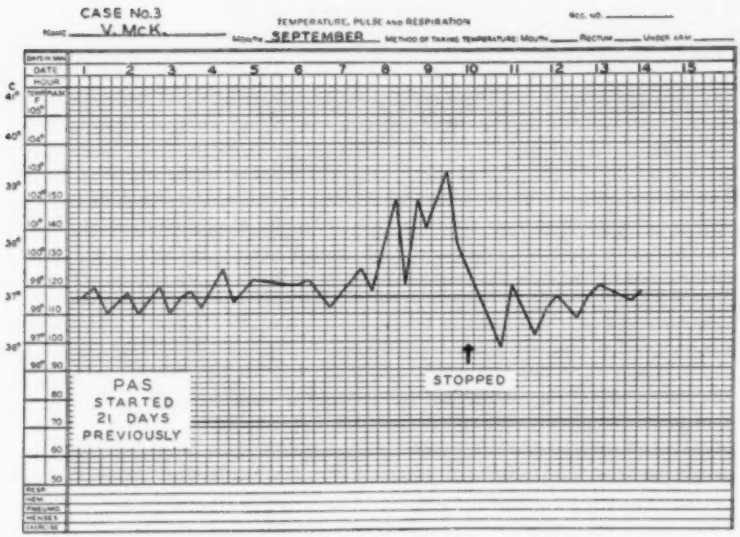

FIG. 3. Case 3 (V.McK.) Temperature, pulse, and respiration chart

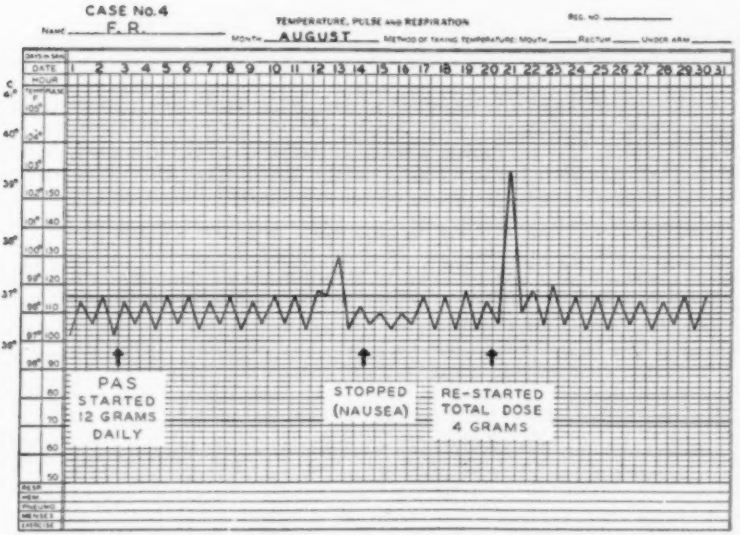

FIG. 4. Case 4 (F.R.) Temperature, pulse, and respiration chart

of 12 Gm. on June 18, 1949 and increased to 16 Gm. on June 23, 1949. Low-grade fever and nausea developed, causing the drug to be discontinued on July 11, 1949. After nine days of rest, it was restarted on July 20, 1949. After the patient had taken 8 Gm., less than one average daily dose, temperature rose to 103.4°F., with chills, violent nausea, and epigastric distress. The temperature promptly subsided upon discontinuance of the drug, but the patient lost ten pounds and did not regain a sense of well-being for one month.

Case 2. F. S., a 26-year-old man, had pulmonary tuberculosis, III-B, bilateral, with a tension cavity in the right lung. He had received no previous antimicrobial therapy. Streptomycin and PAS were started simultaneously on May 16, 1949. The dosage of PAS was 12 Gm. daily, of streptomycin 1 Gm. three times a week. PAS was increased to 16 Gm. daily on June 2. On June 7, 1949, the temperature rose to 104°F., with vomiting and pruritis. Both drugs were stopped and all symptoms cleared. No other cause for the fever could be found, the roentgenogram remaining unchanged. On June 11, 1949, a single dose of PAS of 4 Gm. without streptomycin was given. The temperature rose to 103°F., with vomiting and pruritis. PAS was stopped permanently and the symptoms cleared.

Case 3. V. McK. had pulmonary tuberculosis, III-B, bilateral, with an inexpansible lung on the right and scattered exudative and cavitary disease on the left with recent left pneumothorax. PAS was started August 10, 1949 at 9 Gm. daily. Symptomatic improvement occurred. On September 8, 1949, the patient became ill with fever and malaise. It was at first suspected that an effusion was developing in the left side, but this did not occur. Careful physical and neurologic examination and urinalysis revealed no cause for temperature. The blood count was as follows on September 12: hemoglobin 70 per cent; red blood cells 3,700,000 per cu. mm.; leukocytes 3,300 per cu. mm. The respective percentages in the differential count were: eosinophils, 4; basophils, 2; segmented forms, 66; lymphocytes, 28. The PAS was discontinued on September 10. The temperature fell to normal on September 12. No change appeared in the roentgenogram.

Case 4. F. R., a 34-year-old man, had pulmonary tuberculosis, III-A, with right thoracoplasty. On August 3, 1949, PAS in a daily dosage of 12 Gm. and streptomycin, 1 Gm. three times a week, were started. PAS was stopped August 15 because of temperature elevation to 100° F., with nausea, but the administration of streptomycin was continued. All of the symptoms cleared. On August 21, 1949, PAS was restarted. After one dose of 4 Gm. the temperature rose to 103°F., with severe nausea and malaise. PAS was stopped and was never restarted. The temperature fell to normal promptly while the gastrointestinal symptoms cleared gradually.

COMMENT

From these and similar but less clearcut reactions, it appears that patients receiving PAS may be subject to a type of sensitization reaction which causes the febrile episode shown in the above protocols. It is probably more than coincidence that in 3 of these 4 cases the initial reaction occurred between three and four weeks after beginning administration of the drug. The violent onset of symptoms and immediate elevation of temperature within a few hours after the beginning of re-treatment leaves no doubt in our minds that the drug was the exciting factor. As a result of these experiences, we have ceased any attempt to re-treat patients who have shown this type of response, although second courses of treatment are feasible in patients who have displayed nausea, vomiting, diarrhea, transient eruptions, and mild bone marrow depression.

SUMMARY

An acute toxic reaction, characterized by temperature above 103°F. and accompanied by severe prostration, nausea, and vomiting, was observed in 4 of 85 (4.6 per cent) patients under treatment with para-aminosalicylic acid. In 3 of the 4 instances, this reaction recurred after the initial dose of an attempted second course of treatment and subsided promptly following withdrawal of the drug.

It is suggested that patients who have exhibited minor toxic symptoms during a first course of treatment with para-aminosalicylic acid be carefully observed for such reactions should a second course be found necessary.

SUMARIO

Reacciones Febriles al Acido Para-Aminosalicílico

En 4 (4.6 por ciento) de 85 enfermos en tratamiento con ácido para-aminosalicílico, observóse una reacción tóxica aguda, caracterizada por fiebre de más de 39.5°C. y acompañada de agotamiento intenso, náuseas y vómitos. En 3 de los 4 casos, dicha reacción recurrió consecutivamente a la dosis inicial de otra proyectada tanda terapéutica y cedió rápidamente después de suspenderse la droga.

Indícase que los pacientes que hayan manifestado síntomas tóxicos de menor cuantía durante la primera serie de tratamiento con el ácido para-aminosalicílico sean observados cuidadosamente con respecto a dichas reacciones, de resultar necesaria otra serie de terapéutica.

SPREAD OR EXACERBATION OF PULMONARY TUBERCULOUS LESIONS AS A RESULT OF THORACOPLASTY[1]

STEPHEN C. H. YANG AND WILLIAM M. LEES

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INTRODUCTION

This article is concerned with the fate of those patients who developed a spread, reactivation, or exacerbation of their pulmonary tuberculosis after extrapleural thoracoplasty. During the 10-year period from January 1, 1934 to January 1, 1944, 317 patients from the Michigan State Sanatorium, Howell, Michigan, were referred to the University of Michigan Hospital, Ann Arbor, Michigan, for thoracoplasty. A total of 1,388 stages were performed on this group without the benefit of streptomycin or penicillin. Thirty-four patients had thirty-five pulmonary spreads or exacerbations of their tuberculosis within two months of a stage of the thoracoplasty. Exacerbations occurred in one patient after the second and sixth stages of her thoracoplasty, making a "spread rate" of 10.7 per cent in the entire series of patients.

Roentgenographic evidence of a new infiltration is the only criterion used in determining the appearance of a spread or dissemination. The term "spread" refers to a bronchogenic, pneumonic infiltration appearing in any area of either lung where no lesion had been found before thoracoplasty. An inactive lesion in any part of the lung, becoming active again after thoracoplasty, is a "reactivation." A previous active lesion, either progressive or regressive, becoming larger after thoracoplasty is an "exacerbation." For the sake of continuity throughout this report, the terms *spread*, *reactivation*, and *exacerbation*, unless otherwise indicated, will be referred to under the general term of *spread*.

REVIEW OF LITERATURE

Search of the literature discloses very little concerning tuberculous spread following thoracoplasty. Such spreads were emphasized by Alexander (1) in 1937. Adams and Dufault (2) reported 12 exacerbations in 241 patients (604 stages). Schaffner and Found (3) noted 10 spreads following 335 stages. Harrison and Berry (4) observed 16 spreads in 150 patients (430 stages). More recently, Parke, Loftus, and Bishop (5) reported a series of 81 spreads following 805 thoracic operations, including 755 stages of thoracoplasty. Their report concerned itself with 367 patients with active, advanced cavitary disease. Kinsella *et al.* (6) had 90 patients with spreads or reactivations among 613 patients (1,574 stages); their operative incidence of spread was 6.34 per cent. Postoperative spread was a factor in the subsequent death of the majority of the patients who died within two years.

Murphy, Walkup, and Cheek (7) observed 28 spreads and reactivations out of 857 stages done on 316 patients. In another group of patients, Murphy (8) attempted to determine the efficacy of streptomycin in protecting patients against postoperative spread of

[1] From the Department of Surgery, University of Michigan Hospital, Ann Arbor, Michigan.

their tuberculosis. He analyzed the results of 699 operations on 258 patients who received streptomycin preoperatively and postoperatively for two weeks, in doses ranging from 0.5 to 2.0 Gm. per day. In addition, an analysis was made of 648 operations on 249 patients operated upon during the same period of time without the benefit of streptomycin. In the "protected" group there were 14 spreads (2 per cent per operation or 5.4 per cent per patient) whereas, in the "unprotected" group there were 36 patients with postoperative spread (5.6 per cent per operation or 14.4 per cent per patient).

TABLE 1

Spread of Tuberculosis following Thoracoplasty as Reported by Various Authors

AUTHORS	NUMBER OF PATIENTS	NUMBER OF OPERATIONS	SPREADS			
			Per patient		Per operation	
			Patients	Per cent	Spreads	Per cent
Adams and Dufault (1941)	241	605	12	4.9	12	1.98
Schaffner and Found (1942)	?	335	10	—	10	2.9
Harrison and Berry (1943)	150	430	16	10.7	16	3.95
Parke, Loftus and Bishop (1948)	367	805*	81	22.0	81	10.0
Kinsella, *et al.* (1949)	613	1,574	90	14.66	94	6.34
Murphy, Walkup, and Cheek (1948)	316	857	28	8.86	28	3.1
Murphy (1948)						
Streptomycin and thoracoplasty	258	699	14	5.4	14	2.0
Control group, no streptomycin	249	648	36	14.4	36	5.6
Present series	317	1,388	34	10.7	35	2.5

* Of the 805 thoracic procedures, 755 were thoracoplasties and 50 were lobectomies, cavernostomies, thoracotomies, and extrapleural pneumothoraces.

Methods

SELECTION OF CASES

A majority decision of the medical-surgical conferences[2] determined the surgical procedure used for the patients who are the subject of this report. The decision was reached following a review of the history, the physical and laboratory findings, and all of the roentgenograms of each patient. The patient was presented in person at the conference.

The classification of disease conformed with that now listed by the National Tuberculosis Association. This was made on the basis of the disease in evidence in the immediate preoperative roentgenograms, and not by the film taken at the time of the original admission to the sanatorium. The entire series of roentgenograms of each case were, however, reviewed and re-evaluated by the authors.

[2] Combined conferences of University Hospital thoracic surgeons and the medical staff of the Michigan State Sanatorium.

OPERATION

The preparation for surgery, the operative technique, and the postoperative care were carried out according to the principles presented in 1937 by Alexander (1). Most of the anterior-stage thoracoplasties were of the Haight (9) type; a few were of the Bisgard type or a combination of the two.

From 1934 to 1938 the anesthesia was a combination of nitrous oxide, ether, and oxygen inhalation, plus local infiltration of 0.5 per cent procaine. From 1938 to 1944 cyclopropane, supplemented with 0.5 per cent or 0.25 per cent metycaine, or 0.5 per cent procaine, was used almost exclusively. In a few patients with a very poor prognosis, local anesthesia alone was used. Ether vapor and oxygen have been largely used since this series of patients was operated upon.

Preoperatively, the patient was instructed to empty secretions from the bronchial tree by coughing and postural drainage. After the patient reached the anesthesia room, he was placed in a 10-degree Trendelenberg position for 10 to 15 minutes before induction of the anesthesia. After the induction of anesthesia the patient was placed in the lateral decubitus position in a 10-degree Trendelenberg position with the side to be operated on uppermost. Bronchial secretions were thus encouraged to flow toward the pharynx by gravitation. They also tended to spill into the most dependent portion of the contralateral lung, i.e., the upper lobe. An endotracheal tube was used only rarely. It is our practice to use a hard rubber airway and an air-tight mask. The anesthetist undertakes to have the patient nearly awake by the time the dressing is applied. At this time careful aspiration of pharyngeal secretions is performed. In the immediate postoperative period the patient is made to clear the bronchial tree repeatedly of all secretions by cough; the evacuation of these secretions aids in preventing bronchogenic spread of tuberculosis.

The usual interval between stages was three weeks. Postponement of the next intended stage, when necessary, was usually due to a spread or, in a few instances, wound infection, dyspnea, or poor general condition. Delay of the next stage depends chiefly upon the extent of the spread or exacerbation, the severity of symptoms, and the rapidity of their disappearance. In a few instances, thoracoplasty was completed without interruption in spite of the roentgenographic evidence of a spread. In most of the spreads, the next stage of thoracoplasty was delayed from one to eight months, or further stages were abandoned altogether because of the severity of the spread.

The number of ribs to be removed in each patient depended on the size and location of the pulmonary cavity. In order to get complete closure of a tuberculous cavity, at least one rib below the level of the visible lesions was resected. A sufficient number of ribs (usually seven) were removed to cause the scapula to drop in and aid the collapse, but the number of ribs removed varied with the individual case.

OBSERVATIONS

ANALYSIS OF CASES

Pulmonary tuberculous spread, reactivation, or exacerbation were encountered 35 times in 34 patients in a series of 317 patients on whom 1,388 stages of thoracoplasty were performed. This represents a spread rate of 10.7 per cent per patient, or 2.5 per cent per operation. Eleven spreads occurred in areas not previously involved by the disease, 14 were reactivations, and 10 were exacerba-

tions of previous lesions. In the last two groups, it was difficult to determine in a few cases whether a reactivation or an exacerbation had taken place.

The 34 patients with spread had a total of 142 stages of thoracoplasty, an average of four stages for each patient. They included 116 posterolateral, 20 anterior, and 6 revision operations. In addition, a partial scapulectomy was done three times.

Sex, age, and race: Among the 34 patients there were 16 men and 18 women. This was comparable to the sex division in the entire 317 cases. The age range for the men was from 16 to 51 years, and for the women, from 14 to 53 years. There were 2 Negroes and one American Indian in the series.

Duration of disease: Eighteen patients had had tuberculosis from one to two years, 7 from two to three years, 3 from three to five years, and 6 from five to sixteen years. The duration of the disease before thoracoplasty showed no definite influence on the incidence and extent of spread or exacerbation after surgery.

Sputum: All but one of these 34 patients had tubercle bacilli in the sputum or gastric contents at the time thoracoplasty was begun. Thirty were positive for tubercle bacilli on smear, one on concentration of a pooled sputum specimen, one on sputum culture, and one on culture of gastric washings.

The daily quantity of sputum raised in twenty-four hours varied from less than 5 cc. to approximately 300 cc. when thoracoplasty was started. One patient raised no more than 5 cc.; 18, 6 to 25 cc.; and the remainder of the patients raised more than 25 cc. Those who raised more than 25 cc. of sputum tended to develop a more extensive spread.

Stage of disease before thoracoplasty: All 34 patients who had a spread following thoracoplasty had advanced pulmonary tuberculosis at the time surgery was begun (table 2). Seven were rated as moderately advanced, and 27 as far advanced cases. All but 2 patients had bilateral disease. The 2 patients with unilateral disease had far advanced lesions.

In the moderately and far advanced groups, 43 and 46 per cent, respectively, developed small spreads. In the far advanced group, there were almost twice as many extensive spreads (22 per cent) as seen in the moderately advanced group (14 per cent).

Type of pulmonary tuberculosis: Among the 34 patients, 24 (70 per cent) had a mixed type of pulmonary tuberculosis, most of the 24 being of the productive type (table 3). There were 5 (15 per cent) cases of productive, 3 (9 per cent) pneumonic, and one exudative type of tuberculosis. One patient had a tuberculous empyema with a broncho-pleuro-cutaneous fistula.

There were 4 patients with preoperative atelectasis in the ipsilateral lung (upper lobe), but none of these cases developed an extensive spread nor did any of them die from the spread.

Of the 7 extensive spreads, 5 occurred in cases with a mixed type of tuberculosis, one in a pneumonic, and one in a productive type of disease. Cases with the mixed type of lesion commonly had large cavities. This is the probable reason for the more extensive spread found in this type of disease.

Pulmonary Cavity

In the study of the preoperative roentgenograms of this series a record was made of the diameter, location, shape, number, and the approximate thickness of the wall of the cavities.

Diameter of pulmonary cavity: All but 2 of the 34 patients had one or more pulmonary cavities varying from one to more than 10 cm. in the longest diam-

TABLE 2

Stages of Pulmonary Tuberculosis and Spread

STAGE OF DISEASE	NUMBER OF CASES	EXTENT OF SPREAD						NUMBER OF SPREADS
		Small		Moderate		Extensive		
		Number	Per cent	Number	Per cent	Number	Per cent	
Minimal	—	—	—	—	—	—	—	—
Moderately advanced	7	3	43	3	43	1	14	7
Far advanced	27*	13	46	9	32	6	22	28
Total	34	16	46	12	34	7	20	35

* One patient had an exacerbation twice, one small and one extensive.

TABLE 3

Type of Disease and the Extent of Spread

TYPE OF DISEASE	NUMBER OF CASES	PER CENT	EXTENT OF SPREAD			NUMBER OF SPREADS
			Small	Moderate	Extensive	
Mixed	24*	70	10†	10†	5	25
Productive	5	15	3	1	1	5
Pneumonic	3	9	2	—	1	3
Exudative	1	3	1†	—	—	1
Empyema	1	3	—	1	—	1
Total	34	100	16	12	7	35

* One patient had an exacerbation twice, one small and one extensive.

† Each such sign represents an individual case of atelectasis which developed before thoracoplasty.

eter (table 4). Cavity size is here stated as the sum of the diameters of all the cavities. Eleven had cavities less than 4 cm. in total diameter and none had an extensive spread. All seven extensive spreads occurred in patients who had cavities with a diameter greater than 4 cm.

Location of cavity: In table 5 are listed the location of the cavities and the extent of the spread of tuberculosis following thoracoplasty. In 6 patients the cavities were located in the apical or supraclavicular area of the lung. The cavities in this group were less than 4 cm. in diameter. Eleven patients had cavities in the infraclavicular area and 2 of them had extensive spreads. In the group of

12 patients with cavities occupying both apical and infraclavicular areas, 4 had extensive spreads. One of these patients had two exacerbations. There was only one case with a cavity (4 cm. in diameter) in the mid-lung field. This patient had a small spread. Two patients had cavities scattered throughout an entire lung. One of these had a moderate and the other had an extensive spread. Two patients who had no cavity did not have an extensive spread. It is of significance to note that 6 of the 7 extensive spreads occurred in patients with cav-

TABLE 4

Diameter of Pulmonary Cavity and Spread

DIAMETER OF CAVITY	NUMBER OF CASES	EXTENT OF SPREAD			NUMBER OF SPREADS
		Small	Moderate	Extensive	
1 to 4 cm.	11	5	6	—	11
5 to 12 cm.	21*	10	5	7	22
No cavity	2	1	1	—	2
Total	34	16	12	7	35

* One patient with a 7 cm. cavity had a small exacerbation after the second stage and an extensive exacerbation after a sixth posterolateral stage of thoracoplasty.

TABLE 5

Location of Cavity and Spread

LOCATION OF CAVITY	NUMBER OF CASES	EXTENT OF SPREAD			NUMBER OF SPREADS
		Small	Moderate	Extensive	
Apical	6	4	2	—	6
Infraclavicular	11	4	5	2	11
Apical and infraclavicular	12*	6	3	4	13
Mid lung	1	1	—	—	1
Entire lung	2	—	1	1	2
No cavity	2	1	1	—	2
Total	34	16	12	7	35

* One patient had an exacerbation twice, one small and one extensive.

ities either in the infraclavicular area or the apico-infraclavicular area. The other extensive spread developed in the patient with cavities throughout the lung, including the infraclavicular area. Apical cavities alone were not a cause of extensive spread following thoracoplasty in this series.

Shape of cavity: Sixteen patients had round, 10 had oval, and 6 had irregularly shaped cavities (table 6). Two patients had no cavity. In the group with irregularly shaped cavities, there were more moderate and extensive spreads than in other groups.

Prethoracoplasty roentgenograms showed a fluid level in the cavities of 7 of the 34 patients on one or more occasions. None of these cavities was irregular

in shape (table 6). One of the 7 patients had two spreads, making a total of eight spreads.

Number of cavities: All but 2 of the 34 patients had cavities before thoracoplasty. It is interesting to note that in the group of 17 patients with one cavity only 2 of them developed an extensive spread following surgery. In 8 patients with two to four cavities, there were no extensive spreads; whereas in the small group of 7 patients with five or more cavities, there were five extensive spreads. As mentioned previously, the extent of postoperative spread increased directly with the diameter as well as the number of pulmonary cavities.

Type of cavity wall: The relationship of spread to the thickness of the cavity wall and the degree of infiltration around it are listed in table 7. Twenty (59 per cent) patients with thin-walled cavities had spreads; 12 (35.1 per cent) patients with thick-walled cavities and 2 patients with no cavities had spreads.

TABLE 6

Shape of Cavity and Extent of Spread

SHAPE OF CAVITY	NUMBER OF CASES	EXTENT OF SPREAD			NUMBER OF SPREADS
		Small	Moderate	Extensive	
Round	16	7	7	2	16
Oval	10*	7	1	3	11
Irregular	6	1	3	2	6
No cavity	2	1	1	—	2
Cavity with fluid level present at some time	(7)*	(4)	(2)	(2)	(8)
Total	34	16	12	7	35

* One patient had an exacerbation twice, one small and one extensive.

A round or oval cavity with thin walls suggests the presence of tuberculous bronchitis, even if bronchoscopies are negative. Bronchitis might be present only in small bronchi where visualization through a bronchoscope is impossible. Of the seven extensive spreads, five were in patients who had round or oval thin-walled cavities and two were in patients with round or oval thick-walled cavities. The various degrees of infiltration around the cavities apparently had no influence upon spread.

Tuberculous Tracheobronchitis

Tuberculous bronchitis is said to be an important cause of spread. In this series of 317 thoracoplasty patients, 75 (23.6 per cent) had varying kinds and degrees of such lesions at the time of surgery and 242 (76.4 per cent) had none. Nine (12 per cent) of the 75 patients with tracheobronchitis and 25 (10 per cent) of the 242 patients without such lesions developed spread or exacerbation during thoracoplasty. This shows that, in this series, those patients with tracheobronchial disease when subjected to thoracoplasty had only a 2 per cent greater risk with regard to pulmonary spread or exacerbation than the patients who did not

have such a lesion. It was noted that the site of tracheobronchitis did not influence the extent of spread, but the extent and type of bronchial involvement bore an apparently important relationship to pulmonary spread.

Type of tracheobronchial lesion: At the University of Michigan Hospital the lesions of tuberculous tracheobronchitis are classified into four types: (*1*) redness with submucosal infiltration and edema; (*2*) ulceration; (*3*) granulation with or without hyperplasia; and (*4*) fibrostenosis. The various degrees of spread were found more or less evenly distributed in the different types of tracheobronchial lesions in this small group of patients. Usually, however, thoracoplasty should not be performed in groups (*1*), (*2*), and (*3*) unless a series of bronchoscopic examinations shows that the activity of the bronchial or tracheal lesion is decreasing or, at least, that it is not progressive.

TABLE 7

Type of Cavity Wall and Its Surrounding Infiltration in Relation to Spread

TYPE OF CAVITY WALL AND INFILTRATION	NUMBER OF CASES	EXTENT OF SPREAD			NUMBER OF SPREADS
		Small	Moderate	Extensive	
Thin-walled cavity:	20				20
Slight infiltration		2	3	2	
Moderate infiltration		4	1	2	
Heavy infiltration		2	3	1	
Thick-walled cavity:	12				13
Slight infiltration		2	2	—	
Moderate infiltration		3*	—	1*	
Heavy infiltration		2	2	1	
No cavity	2	1	1	—	2
Total	34	16	12	7	35

* One patient had an exacerbation twice, one small and one extensive.

Site of tracheobronchitis and the location of spread: Among the 9 patients with tracheobronchitis who developed a spread following thoracoplasty, 8 had ipsilateral bronchitis and developed the spread in the contralateral lung. One patient with bilateral upper lobe orifice bronchitis and laryngitis had a very extensive contralateral spread. It is interesting that none of these patients had a spread in the lung which was drained by the diseased bronchus. This was probably because of the dependent position of the contralateral lung on the operation table and the pooling of the bronchial secretions in that lung.

Site of tracheobronchitis in relation to parenchymal lesions and cavities: All 9 patients with tuberculous bronchitis prior to operation had bilateral parenchymal tuberculosis. Without exception, the bronchial lesions were located in the bronchi draining the corresponding portions of the lung which were most diseased.

Preoperative Therapy

Before thoracoplasty, collapse therapy of one form or another had been used in most of these patients in an attempt to close pulmonary cavities and to convert the sputum. There was an exacerbation of lesions in the contralateral lung following thoracoplasty in 6 patients who had previously received pneumothorax treatment of the contralateral lung which had been abandoned at the time of surgery. Contralateral exacerbations of this sort occurred on seven occasions as there were two exacerbations in one patient. Three of these exacerbations were extensive, two moderate, and two small. The possibility of extensive spread in these 6 patients was considered preoperatively, since they not only had extensive disease in the ipsilateral lung, but also an active lesion in the contralateral lung severe enough to have required collapse therapy.

Contralateral Disease

When the contralateral lesions were considered separately from those of the ipsilateral side, 15 were minimal, 16 were moderately advanced, and one was far advanced. Two patients did not have contralateral disease. Nine of the contralateral lesions were active, either progressive or regressive, before thoracoplasty, while the others were apparently inactive. It is of interest to note that all 9 patients with an active contralateral lesion before thoracoplasty developed an exacerbation in that lung after the operation. One patient had two exacerbations, one after the second and the other after the sixth stage. Thus, there was a total of ten exacerbations. None of the cases with inactive contralateral lesions developed exacerbations.

LATE RESULTS

Of the 34 patients who had spread after thoracoplasty, 15 are now dead (table 8). Nineteen patients survived the spread, the interval since spread being from six to fifteen years.

Deaths: Two of the 15 deaths came within three months after thoracoplasty and 13 afterward. Twelve of the deaths were due to tuberculosis and 3 to other causes (table 9).

Regarding the time of death following the occurrence of spread, 6 were dead within one year. Only one of these deaths was considered an operative death and it occurred on the eighteenth postoperative day. In the second year following the spread there were 4 deaths; from the third to the fifth year, 3 deaths; and from the sixth to the tenth year, 2 deaths. The majority of patients who died of tuberculosis did so within two years after the spread, and the rest died within four and one-half years.

Causes of death: Among the 12 deaths due to tuberculosis (table 9), one patient was unable to cough or expectorate after a third stage of thoracoplasty. Bronchoscopic aspiration to remove secretions was carried out seven times, but he developed an extensive bilateral pulmonary spread and a *Staphylococcus* wound infection. He died with auricular fibrillation on the eighteenth postoperative day. Eight patients eventually died of their tuberculous spread. One patient with a large cavity which was not closed by thoracoplasty developed a spread

following his surgery. Six months later an upper lobe lobectomy was performed for the cavity under the thoracoplasty after the spread was thought to be controlled, but death occurred five months after the lobectomy from progression of the disease.

TABLE 8

Late Results of Spread

1934–1949

Death subsequent to spread:		15 cases
1 to 3 months	2	
4 to 12 months	4	
1 to 2 years	4	
3 to 5 years	3	
6 to 10 years	2	
Survivors after spread:		19 cases*
6 years	1	
7 years	3	
8 years	3	
9 to 10 years	3	
11 to 12 years	5	
13 to 15 years	4	
Total		34 cases

* Recent information was unobtainable in 3 patients, but they were well and doing full-time work at the time of their last examination 8, 10, and 11 years, respectively, after spread.

TABLE 9

Causes of Death

Tuberculous:		12 cases
Operative and spread	1	
Progression of spread and disease	8	
Following lobectomy	1	
Late reactivation	2	
Nontuberculous:		3 cases
Tension pneumothorax with sudden death	1	
Cardiovascular failure	1	
Pneumonia	1	
Total		15 cases

Two patients had late reactivation of pulmonary tuberculosis. One died five years, and the other seven years, after the primary spread.

Three patients died of nontuberculous causes. One had an initial pneumothorax to control a moderate spread in the contralateral lung after a third-stage thoracoplasty. A tension pneumothorax developed. The leak was successfully controlled by continuous intrapleural suction, but the patient suddenly died.

The cause of death was undetermined, but air embolism was believed to be the probable cause. Another patient had a moderate contralateral spread after the first-stage operation, but a four-stage, seven-rib thoracoplasty was completed and the spread became resolved within six months. Cardiovascular failure with peripheral edema was the cause of death three years later. The third patient developed a small spread in the contralateral lung following the third stage of thoracoplasty. She was discharged to her home with her disease apparently arrested. An acute nontuberculous penumonia was the cause of death ten years after the spread.

Survivors: Nineteen patients are living, but 3 of them are still in sanatoriums (table 10). Sixteen patients were discharged from the sanatorium with apparently arrested disease. Eleven of the 19 patients who had follow-up examinations from six to fifteen years after their spreads are well and working full time. They all had had a small spread except one patient who had a moderately severe spread. Three other patients are well and doing light housework. Two patients are well, but unable to work; one is dyspneic on exertion, and the other is 64 years old.

TABLE 10

Present Status of Survivors

(6 to 15 years after spread)

Well and working full time	11 cases*
Well and working part time	3 cases
Well but unable to work	2 cases
Residents in sanatoriums	3 cases
Total survivors	19 cases

Three patients who had a spread seven years ago still reside in sanatoriums. One of these patients had an upper and middle lobectomy six years after the spread for a residual cavity under the thoracoplasty, but a bronchopleural fistula and empyema developed. The remaining lower lobe was removed six months later to close the bronchopleural fistula. The empyema is still present but gradually healing. Her last three sputum cultures were negative for tubercle bacilli and her disease is now believed to be arrested for the first time. The other two patients are in sanatoriums. One is improving, but the other is unimproved.

When the present National Tuberculosis Association classification is applied to the 19 living patients, 13 are apparently cured, 4 apparently arrested, one improved, and one unimproved.

"Sputum conversion": Seventeen of the 19 survivors had sputum or gastric cultures negative for tubercle bacilli at the time this survey was made. Two patients still have a "positive" sputum and are residents in sanatoriums.

Comments

In advanced cases of pulmonary tuberculosis there is a tendency toward bronchogenic spread whenever *M. tuberculosis* is present in the secretions. The Vet-

erans Administration (10) reports that the incidence of pulmonary spread of tuberculosis in moderately advanced and far advanced patients treated by bed rest alone is approximately 8 per cent. Upon such patients any major surgical procedure will increase the risk of spread or exacerbation of the pulmonary lesions. Parke, Loftus, and Bishop (11) reported 10 per cent postoperative spread among 282 pulmonary tuberculous patients who had undergone various extrathoracic operations. In a later report, Parke and his associates (5) observed 81 cases of spread in 367 cases of active cavernous pulmonary tuberculosis which had had a total of 805 miscellaneous thoracic operations. When expressed in percentages these figures convert to 22 per cent of the patients or 10 per cent of the operations. Their experience indicates that patients with advanced disease tend to develop a spread more frequently when they are subjected to surgery, particularly thoracic operations.

Bronchial secretions squeezed from the diseased portion of the lung by thoracoplastic collapse are the most important factor in bronchogenic spread. Proper posturing of the patient preoperatively, during the operation, and postoperatively should greatly reduce spread of tuberculosis in that patient. It is suggested that thoracoplasty be performed late in the morning or in the afternoon in order to allow the patient sufficient time to empty his lungs as completely as possible by means of coughing and postural drainage of the secretions which have collected there during the night. Morphine sulfate is used both before and after operation in only sedative doses and not in sufficient quantities to inhibit the cough reflex. During surgery the secretions which collect in the pharynx are aspirated. Postoperatively, the patient routinely lies on his ipsilateral side, but is frequently turned on his back for short periods. He is instructed to cough and expectorate frequently. In the first few days manual splinting of the anterolateral portion of the thorax on the thoracoplasty side by an assistant greatly helps the patient in coughing up bronchial secretions. Later, the patient himself can give support to the chest wall with his hand and arm. The Fowler position is occasionally used to help the patient to cough. It is believed that these precautions greatly reduce the risk of a spread.

Paradoxical motion of the thoracic wall is especially guarded against since in association with so-called mediastinal flutter it can result in a spread because of poor pulmonary ventilation and the resultant retention of bronchial secretions. To guard against this, no more than two and one-half ribs should be removed at any one stage, except in unusual instances.

Any patient who has had a spread, reactivation, or exacerbation of tuberculosis after thoracoplasty and who lives for five years thereafter has an excellent chance of not dying from tuberculosis. In this series, there were only two deaths due to a late reactivation five years after a spread.

Streptomycin, when used adequately, is a relatively effective agent in the control of a spread. But it is our opinion that this drug should not be used routinely for prophylactic purposes in thoracoplasty patients. In this series, without the benefit of this drug between 1934 and 1944, about 90 per cent of the 317 patients did not develop a spread. Furthermore, the hoped-for protec-

tion provided by this drug is not sufficiently certain, under the present methods of administration, to outweigh completely the possible toxic effects and the emergence of resistant strains of tubercle bacilli. It should be reserved for those patients whose disease persists or recurs, at which time it would be of much greater value. Nevertheless, streptomycin has a definite protective value in patients with very extensive disease and bronchial involvement in whom a spread should be especially feared if thoracoplasty were performed. With a course of preoperative streptomycin these patients might be so improved that thoracoplasty could be performed, whereas they might be refused the opportunity of surgery without such improvement. Should a postoperative spread be discovered early, streptomycin is very effective in aiding the resolution of such exudative lesions. Streptomycin may make possible a continuation of the thoracoplasty after a spread.

Summary

1. The records of 34 (10.7 per cent) of 317 patients who developed pulmonary spread, reactivation, or exacerbation of tuberculosis following thoracoplasty have been analyzed. These operations were completed during the ten-year period from 1934 to 1944.

2. There were 35 instances of increased disease in these 34 patients. Among these there were 14 reactivations, 11 spreads, and 10 exacerbations.

3. The relationship of sputum positive for tubercle bacilli, pulmonary cavitation, and tuberculous bronchitis to spread has been discussed.

4. At the end of the second year after spread, 12 (34.3 per cent) patients had complete resolution, 12 (34.3 per cent) had become stabilized, and the rest were either dead or the disease was still progressive.

5. Among the 15 patients who died, 12 died of tuberculosis and 3 died of nontuberculous causes.

6. Nineteen patients are alive from six to fifteen years after spread. Of these, 13 are apparently cured, 4 apparently arrested, one improved, and one unimproved.

Sumario

Difusión o Exacerbación de las Lesiones Tuberculosas Pulmonares como Resultado de la Toracoplastia

1. Analízanse los protocolos de 34 (10.7 por ciento) de 317 enfermos que manifestaron propagación, reactivación o exacerbación de la tuberculosis consecutivamente a la toracoplastia. Esas operaciones fueron llevadas a cabo en el decenio de 1934 a 1944.

2. En dichos 34 enfermos, hubo 35 casos de agravación: 14 reactivaciones, 11 difusiones y 10 exacerbaciónes.

3. Discútese la relación entre positividad del esputo para bacilos tuberculosos, cavernas pulmonares y bronquitis tuberculosa.

4. Al terminar el segundo año consecutivo a la propagación, 12 enfermos (34.3 por ciento) mostraban resolución total, 12 (34.3 por ciento) se habían estabilizado, y los restantes o habían fallecido o se hallaban en vía evolutiva todavía.

5. De los 15 pacientes fallecidos, 12 murieron de tuberculosis y 3 de causas no tuberculosas.

6. Diecinueve enfermos están vivos de seis a quince años después de la difusión. De ellos, 13 están aparentemente curados, 4 aparentemente estacionados, uno mejorado y uno sin mejorar.

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TUBERCULOUS EMPYEMA: CLINICAL COURSE AND MANAGEMENT[1]

With a Review of 146 Cases

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INTRODUCTION

The records of 7,206 cases of pulmonary tuberculosis treated in the Baguley Sanatorium between January 1, 1929 and January 1, 1948 have been reviewed, with particular attention to the question of tuberculous empyema. In this review, the term empyema is used to designate a collection of purulent fluid in the pleural cavity and does not refer to clear or merely turbid fluids.

One hundred forty-six cases of tuberculous empyema occurred during the period under review and were caused in order of frequency by: contraselective artificial pneumothoraces (93 cases); spontaneous pneumothoraces (44 cases); operative removal of diseased lung (2 cases); Pott's disease of thoracic spine (one case); and 5 of the 6 other cases had extensive, caseous, pneumonic disease in the lung prior to the onset of empyema and were probably associated with spontaneous pneumothorax. In the sixth case, minimal parenchymal disease was present when a greenish pleural fluid appeared which persisted and after many months became purulent.

During the period under review, 703 artificial pneumothoraces, which had lasted at least four weeks, were analyzed. Allowing for 26 cases of empyema due to artificial pneumothorax therapy but admitted to the hospital with the empyema established, there were 67 empyemas in artificial pneumothoraces induced in this hospital, i. e., an incidence rate of 9.5 per cent.

Artificial pneumothorax cases in which clear or turbid fluid developed, not classified as empyema by definition, numbered 222, i. e., 31.6 per cent. Only effusions of sufficient amount to warrant aspiration or to cover the hemidiaphragm are included in the study.

Weisman (1936) found effusions in 84 per cent of 150 consecutive artificial pneumothoraces, but from collected cases he reports clear effusion as occurring in 17.1 to 90 per cent of artificial pneumothoraces.

Coryllos (1937) states that straw-colored, nonpurulent, exudates occur in 50 to 70 per cent of all artificial pneumothoraces.

In the present series, 62 and 20.4 per cent of the 7,206 cases admitted were in the R.B.2[2] and R.B.3[2] categories, respectively (Ministry of Health). Similarly 73.7 and 23.1 per cent of the 610 artificial pneumothoraces which did not develop empyema were induced on R.B.2 and R.B.3 cases. The empyemas following artificial pneumothoraces also occurred for the most part in R.B.2 (73 per cent) and R.B.3 (24 per cent) subjects. There is no doubt that the more

[1] From Baguley Sanatorium, Manchester, England.

[2] See Appendix.

serious complications of artificial pneumothorax therapy tend to occur in the more advanced cases.

COURSE OF TUBERCULOUS EMPYEMA

When nonpurulent fluid forms, adequate rest and careful aspirations may cause the fluid to abate, and the artificial pneumothorax may be continued. Sometimes obliterative pleuritis follows. Rarely the fluid persists and after a variable period, even after a year, slowly changes its character to pus. Other empyemas start abruptly with nonpurulent fluid present for a very short time measured in days or weeks before the onset of pus. Tubercle bacilli may be the only organisms in the pus; in other cases a "mixed infection" of tubercle bacilli and other pyogenic organisms may be present and in those the prognosis is very much worse than in the former cases. The percentage of effusions which eventu-

TABLE 1

Bacteriologic Findings in Empyema Fluids

PERIOD STUDIED	ALL CASES STUDIED	CASES WITH CLEAR FLUID ALWAYS		CASES OF PURE TUBERCULOUS EMPYEMA	CASES OF PURE TUBERCULOUS EMPYEMA PROGRESSING TO MIXED INFECTION	CASES OF MIXED INFECTION FROM THE OUTSET
		Tuberculin positive	Tuberculin negative			
January–June, 1944	17	1	10	3	—	3
July–December, 1944	14	2	10	1	1	—
January–December, 1945	63	15	37	2	3	6
January–December, 1946	66	7	48	7	—	4
January–December, 1947	49	1	24	11	1	12
Total	209	26	129	24	5	25

ally become purulent is variously listed as: 18 per cent (Coryllos), 21 per cent (Hayes), and 16 per cent (Dumarest and Brette).

Contrary to the statements in some texts that microorganisms introduced at aspiration often determine the onset of a mixed infection empyema, the writer believes that, in the absence of intubation or chest wall sinuses, most secondary infection is from the bronchial tree and is associated with bronchopleural fistulae. Small fistulae probably communicate with alveoli which are free from secondary organisms. Larger fistulae often can be shown to connect with septic cavities or the larger bronchi, and secondary infection thus easily reaches the pleural space. Pleural gas analysis supports these beliefs, as does post-mortem examination.

In table 1 may be seen the bacteriologic findings in the examination of samples of pleural fluids from 209 patients who were in this sanatorium or an adjacent military wing. Several samples of fluid from each patient were sent to the laboratory.

In searching for tubercle bacilli, the centrifuged sediment of the sputum de-

posit which collected overnight was stained by the Ziehl-Neelsen method. No guinea pig inoculations or cultures were done as a routine. The use of the latter methods would certainly have increased the yield of fluids positive for *M. tuberculosis* as has been so ably shown by Close (1946), Tergolina (1946), and many others.

In 24 of the cases of empyema the fluid remained solely tuberculous throughout the course of the illness. In only 5 of the cases was there evidence of the progression of a tuberculous empyema of several months' standing to a "mixed infection" empyema. Twenty-five patients had "mixed infection" empyema from the start or from an early period measured in days or weeks from the onset. This rather suggests that a wide communication existed at the outset between pleura and large or medium-sized bronchi.

TABLE 2

Bacteriologic Findings in Mixed Infection Empyema

TYPE OF ORGANISM	FREQUENCY OF OCCURRENCE
Coagulase positive *Staphylococcus aureus*	15
Diphtheroid organisms	10
S. albus	7
Coliform organisms and *B. proteus*	7
Nonhemolytic *Streptococci*	3
H. influenzae	1
B. pyocyaneus	1
S. citreus	1
Hemolytic *Streptococci*	1
Vincent's fusiform bacilli and spirochetes	1
Nonhemolytic, anaerobic *Streptococci*	1

In table 2 is indicated the relative frequency with which the various organisms causing secondary infection occurred. Many cases had more than one type of organism present.

As mentioned above, a clear or turbid, but nonpurulent, pleural effusion associated with artificial pneumothorax may change its character and become purulent after several months. Not infrequently, however, the onset is more dramatic and resembles the situation when a spontaneous pneumothorax is added to an artificial pneumothorax. Many examples of this were noted in the present series. The patient complains of dyspnea which may occur after exercise or a coughing bout, or may occur while he is resting in bed. In some minor cases, the discomfort passes in a few hours; in others, the intrapleural pressure rises and is accompanied by increasing dyspnea. Shock may be present. Fluoroscopic examination reveals that the lung is more collapsed than usual and there is often considerable mediastinal shift to the opposite side. A prompt elevation of temperature occurs. Hutchinson and Blair (1926) were among the first writers to illustrate the coincidence of a steep initial rise of temperature with the first symptoms of added lung rupture in artificial pneumothorax therapy.

There is usually a gradual fall to normal temperature in about one week. If the lung rupture has been severe, however, as following slough of a part of a cavity wall which has been devitalized by the heat of a cautery, there may be no return of the temperature to its previous level and the onset of empyema is rapid. If the empyema persists, the toxemia usually progresses, the temperature remains elevated with marked deterioration in the patient's general condition, and death results. The mediastinum, if not fixed, is pushed to the opposite side and the lung on the affected side becomes progressively collapsed and airless. Edema of the lower chest wall may be seen and empyema necessitatis may develop.

In empyema of longer duration, the pus may gain access to an intercostal space and burrow along the line of intercostal vessels to present at the border of the sternum anteriorly or posteriorly near the outer border of the erector spinae muscles, or in the posterior axillary line. In rare cases pus may rupture into the esophagus.

If the pus becomes encysted and the pleurae greatly thickened, toxemia may be less marked, and in some instances the patient will be able to walk about and even do a certain amount of work. Chandler (1942) mentions cases where such encysted empyema remained for twenty years, the patient remaining in perfect health. Occasionally the pus is calcified into a firm, chalky plaque.

Frequent needling of an empyema has several dangers, the chief of which is sinus formation in the chest wall. Rarely, secondary infection is introduced at aspiration or follows in any event if a sinus appears.

Slowly, as the cachexia continues, the visceral and parietal pleurae thicken and the mediastinum becomes fixed. The extrapleural fascia becomes organized and deformity ensues. The ribs crowd together and become triangular in section and, as may be seen at operation, are adherent to their periosteum. The spine curves with a concavity toward the side of the lesion. (The deformity is the opposite of that which may follow thoracoplasty.)

Amyloid disease may be a complication where there are long-persisting sinuses with secondary infection of the pleural cavity.

Finally, it should be mentioned that very rarely the pus may be gradually absorbed or may be kept in check by frequent aspirations, until the underlying lung re-expands and the empyema ceases to exist.

CASE MORTALITY

The above clinical picture shows the severity of the condition under discussion. Table 3 shows the over-all mortality *irrespective of the type of treatment adopted* in 105 cases, i. e., all empyemas following spontaneous pneumothorax, except one which had operative treatment, are excluded from the total of 146 empyemas under review.

In all, 43 patients were discharged or left against advice following treatment for empyema and had to be followed up through various chest clinics. Only one patient was lost from observation.

Only 20 patients (19.05 per cent) of the total recovered completely from the

empyema. In two instances there was improvement in the patient's general condition, but a chest wall sinus, necessitating daily dressing, remained until April 3, 1948 (the most recent follow-up observation).

The patient, who could not be traced (No. C), was deteriorating rapidly when she left against advice of the staff, and her prognosis was extremely poor.

TABLE 3

Case Mortality of Tuberculous Empyema

	NUMBER OF CASES	PER CENT DISTRIBUTION	SPECIAL CASE NUMBERS
Dead less than 5 years after empyema onset	71	67.6 } 74.3	
Dead five years or more after empyema onset	7	6.7 }	
Recovery from empyema	20	19.05	
Improvement (sinus remained, April 3, 1948)	2	1.9	A, B
Lost from observation and deteriorating	1	.95	C
Empyema persisting April 3, 1948	4	3.8	D, E, F, G
Total	105	100.0	

TABLE 4

Persistent Tuberculous Empyema

CASE NUMBER	DURATION OF EMPYEMA TO APRIL 3, 1948	REMARKS AND PROGNOSIS
B	9 years	Fairly good prognosis; patient well with chest wall sinus.
A	13 years	Patient fairly well but of poor color; does housework; persisting sinus in chest.
F	6 years 1 month	Poor prognosis; chest wall sinus; edema of ankles and albuminuria.
D	2½ years	Poor prognosis; general condition deteriorating.
G	5 years	Poor prognosis; general condition deteriorating.
E	2 years 8 months	Rapid deterioration; bad prognosis.

Seventy-one patients (67.6 per cent) died within five years of the onset of the empyema. Six patients still had empyema on April 3, 1948 and their condition is shown in table 4.

Thus, on the whole, the prognosis of tuberculous empyema is gloomy. Most cases can be prevented but, if they do arise, extremely energetic measures of treatment are called for from the start.

TREATMENT

The treatment of tuberculous empyema is a most controversial subject, but in broad lines it may be stated that there are four main approaches to the problem:

(a) Aspiration only when the fluid by its pressure and volume is causing dyspnea or cardiac embarrassment.

(b) Aspiration at regular and frequent intervals. Modifications of this are aspirations resulting in high, terminal, negative, intrapleural pressures; the use of continuous negative suction; or the use of chemotherapeutic agents systemically or in lavage of the intrapleural cavity.

(The methods listed above can be designated *conservative methods* of treatment.)

(c) The use of surgical methods, extensive thoracoplasty, and plastic operations, decortication, et cetera, after conservative methods have had an extended trial usually for many months or even years.

(d) *Early* use of surgical methods, i.e., within a matter of weeks of the onset of empyema.

Rosenblatt (1947) cites his results in 51 patients with tuberculous empyema treated conservatively and concludes that it is a mistake to say that the patient is doomed if he does not submit to surgery. Chandler's (1942) opinion that these patients should be left alone unless there is some very definite reason for intervention is well known. On the other hand Brock (1943), Hoyle (1943), Coryllos (1937), and many others advocate surgical measures of treatment. Moreover, Klassen, Miller, and Curtis (1946) state that in their experience aspiration and irrigation alone have been of no apparent value in the treatment of empyema.

It is the writer's opinion that only early surgical treatment is of any value and the results of the present review support this conclusion.

Conservative treatment: In the present series, 90 cases of tuberculous empyema were treated by conservative methods (table 5). If groups E and F in table 5 are included, the total deaths or impending deaths amount to 81.1 per cent. It cannot be denied that this shows a poor prognosis with conservative treatment alone. Only 16 patients (17.8 per cent) had complete recovery from the lesion.

Again it must be stressed that the definition of empyema is pus in the pleural cavity. This must be remembered in comparing the results of different workers. Gibbons (1947) defines empyema as "any collection of fluid in the pleural space, containing bacteria." He reports that he continues pneumothorax for as long as possible and that many of his cases show a spontaneous resorption of the empyema without adverse effect upon the pneumothorax or underlying lung. This has not been the writer's experience with purulent empyema, and it is not the outcome in the early cases of the above series where air replacement of pus was attempted in 21 cases with a fatal outcome in 18 cases.

Woodruff's (1937) definition of empyema does not fit the criteria used in the present study. He classifies as empyema "any turbid pleural fluid in the presence of pulmonary tuberculosis or any fluid containing tubercle bacilli on direct smear." In spite of this lower standard of empyema, his results with conservative treatment are poor. Ornstein and Herman (1946) obtained complete re-expansion of the lung in 48 of the 98 cases they treated by conservative methods but a study of their classification reveals that their definition of empyema includes: (a) nonpurulent, (b) seropurulent, and (c) purulent fluids. In the writer's

experience, the first two types of fluid do not offer the same problems in treatment as purulent fluids.

The number of remedies advocated in the treatment of tuberculous empyema is legion, which tends to prove that no single remedy has been found to be totally satisfactory. For instance, Coryllos (1937) mentions as substances for pleural irrigation: normal saline, colloids of gold, copper or silver, formalin or iodoform in glycerin, lipiodol, ethyl morrhuate, allochrysin, methylene blue, gentian violet, Lugol's solution, myrol, solganol-B, insufflations of the vapor of azote-gomenol, potassium permanganate, acriflavine, trypaflavine, Dakin's solution, vuzin, rivanol, simple oil or oil with gomenol, vaccines, and bacteriophages.

TABLE 5

Empyema Treated by Conservative Measures

	NUMBERS	PERCENTAGE	REMARKS
A. Death under 5 years	66	73.3 } 77.7	Average duration of empyema 20 months
B. Death over 5 years	4	4.4 }	
C. Full recovery	16	17.8	—
D. Improvement and alive on April 3, 1948 with sinus	1	1.1	Duration to date 13 years; fair general condition
E. Lost from observation	1	1.1	Deteriorating on discharge
F. Empyema persisting on April 3, 1948; deteriorating	2	2.3	—

Fishberg (1932) adds lysol and quinine to this list. MacMillan (1947) has used heparin intrapleurally; Paquette (1946) has used mercurochrome; Bruce and others (1946), Diasone and other sulfones; Donaldson and Samuel (1946), tyrothricin; Ornstein and Herman (1946), oxygen, azochloramide, and sodium tetradecyl-sulfate; and Raab (1946) has used sterilized Vitamin A and D concentrate. Coello (1947) has used patient's whole blood with penicillin, O'Brien, Brown, and Pearse (1947), glycerite of hydrogen peroxide (1.5 per cent) containing 0.1 per cent of 8-hydroxyquinoline; and Andosca and Foley (1948) used calcium ribonate and Vitamin C.

Many other drugs are mentioned in the literature, including the latest sulfones and streptomycin (Hinshaw, Feldman, and Pfuetze (1946); Hinshaw, Pyle, and Feldman (1947); Freedlander and French (1947); the report of the American Trudeau Society (1947); and many others).

In the writer's experience, intrapleural instillation of para-aminosalicylic acid has been no more effective than normal saline in the treatment of purulent

tuberculous empyemas, and it has not been possible to repeat the successes of Dempsey and Logg (1947).

Why do conservative methods of treatment yield such poor results? First, it must be recognized that no two cases of tuberculous empyema are exactly alike. The fluids may differ widely in cellular and bacterial contents; there may or may not be chest wall sinuses present; the underlying parenchymal disease may be quiescent or cavitated. The general condition of individual patients differs widely and so does the size of the bronchopleural fistula. In the conservative treatment of empyema, aspirations must be thorough, at intervals of one or two days, and if the size of the bronchopleural fistula permits, the procedure should result in a negative intrapleural pressure. All the rules of asepsis should be observed. A point in the anterior axillary line should be chosen in the event that a sinus forms in the field needed subsequently for a thoracoplasty incision. Moreover, the aspirations should be fairly high so that the needle track is not bathed in the residual pus after aspiration.

Unless there is much fibrin, it is preferable not to irrigate the empyema cavity for there is a real danger of bronchogenic spread of disease to the opposite lung via a bronchopleural fistula when this procedure is used.

Where the aspirations are performed meticulously, in favorable cases the lung will re-expand and the parietal and visceral pleurae stick together and organize. In spontaneous pneumothoraces it is good practice to introduce a Monaldi type of intracavitary suction tube into the pleural space and to apply continual suction to attain this end.

All too frequently, and even with most careful management, the lung re-expands slowly and then remains stationary, often with a narrow peripheral slit of persistent pleural space. If the lung has not completely re-expanded in a very few weeks, say eight at the most, the empyema is probably incapable of being benefited by further conservative measures. In such a situation, a surgical colleague should be consulted at once before the patient's condition deteriorates.

The explanation of such an early impasse is simple. The longer the empyema persists, the thicker the deposit of fibrinous material and curd on the pleural surfaces. It eventually resembles the rind of an orange in thickness and has the appearance of chamois leather. Sections from cadavers and from specimens obtained at operation show that this fibrin is either devoid of new capillaries and granulation tissue or, in very chronic cases, is only invaded by capillaries in the deepest parts next to the lung itself. The periphery of the curd is avascular. When an ordinary tissue wound granulates and the two granulating edges are approximated they usually stick readily, and fibroblastic and capillary bridges soon unite the surfaces firmly. Not so with the pleurae. Several weeks of close apposition of the pleural surfaces are necessary to allow the avascular part of the fibrin bridge to be invaded with granulation tissue. After an empyema has lasted for several months it is almost impossible to attain these conditions by aspiration alone, as breathing, coughing, and the effect of gravity all pull the lung away from the chest wall.

Intubation and continuous suction, in the writer's experience, have been no

better than thorough needling, and in any instance are bad policy unless there is secondary infection present.

Thus every week's delay in attaining lung re-expansion means more pleural thickening and less chance of cure. Two other factors determine a lung's non-expansion: (a) the size of the bronchopleural fistula; and (b) the extent of disease in the lung tissue itself.

Bronchopleural fistula is probably present at some time in every case of tuberculous empyema. Tests for fistula include:

(*1*) Aspiration of the pus followed by withdrawal of air and determination of the resultant negative pressure in the pleura. After half an hour the pressures should be measured again. High negative pressures cannot be maintained with patent fistulae.

(*2*) The introduction of ether into the pleural cavity may be followed quickly by detection of the gas in the nose.

(*3*) The injection of methylene blue into the pleural cavity with subsequent search for the dye in the sputum.

(*4*) Application of Rosen's (1947) observations that sulfonamides give an immediate and stable yellow reaction with Ehrlich's reagent by the introduction of 40 cc. of soluble sulfathiazole into the pleural cavity and collection of sputum into a jar of Ehrlich's reagent. A control jar is necessary as the reagent is itself straw-colored.

(*5*) Retrograde bronchograms can occasionally be made if lipiodol is introduced into the pleural cavity.

The above tests are crude, only demonstrate large fistulae, and may fail if the pleural fluid level covers the opening.

(*6*) Pleural gas analysis is the most scientific method for determining the size and existence of a fistula. It can be done only with an intact chest wall. Davy (1823) was probably the earliest writer on the subject. Coryllos and Birnbaum (1930) and Henderson and Henderson (1932) described the mechanism of gas absorption from alveoli where there was bronchial obstruction and the absorption of gas from any closed space within the body, respectively.

Coryllos, Konterwitz, and Levine (1932) described the clinical application of gas analysis of pleural air and, like Matsuzawa (1937), they demonstrated how to determine the amount of air in the pleural cavity and the method of calculating the absorption index of the pleura.

Ulmar (1937) and Ornstein, Herman, and Friedman (1946) showed that, in determining the onset of bronchopleural fistula, a knowledge of pre-existing gas values in the patient's pleura was necessary and that those values were usually constant for the same person.

Coryllos (1937) presented his conception of the treatment of tuberculous empyema and stated that it was possible to demonstrate three sizes of fistula by gas analysis: punctiform (less than 0.5 mm.), small (less than 1 mm.), and large (1 to 10 mm. or more).

Using the same type of apparatus as Coryllos, the writer has concluded that it is only possible to diagnose large fistulae accurately and that, while the existence of the other fistulae can be proved, they cannot be placed with certainty into groups according to size.

Coryllos rightly points out that it is only in the punctiform fistulae that there is any justification for conservative measures. Even in such a situation, however, there may be failure in obtaining lung re-expansion, because of the extent of disease in the lung parenchyma. Healthy lungs can be compressed and remain capable of re-expansion for long periods. Thus some cases of chronic empyema can be treated by decortication and the lower lobe will, aided by the anesthetist, expand on the operating table. Many of those cases have upper lobe disease before the onset of empyema, and the lower lobes have been comparatively healthy.

When there is extensive roentgenographic mottling in a lung, there is a grave danger that, once collapsed, such a lung will be incapable of ever re-expanding. The writer has recently observed a case in which a spontaneous pneumothorax was added to a right artificial pneumothorax one month after adhesion section. An empyema rapidly formed with secondary infection, and the patient was dead in three months. At autopsy the entire lung was carnified and quite incapable of re-expanding, although the fistula in the upper lobe was minute in size. This lung had exhibited scattered, "soft" mottling in all zones when viewed roentgenographically prior to the artificial pneumothorax induction.

Roentgenographic, "soft" mottling represents areas of caseous bronchopneumonia. The bronchioles and small bronchi around such foci always have thickened walls and semioccluded lumina due to tuberculous changes in their walls. The least alteration of alignment, after the induction of an artificial pneumothorax or the ballooning of a neighboring tension cavity, closes those fine bronchi and leads to atelectasis (shown in the roentgenogram as a ground-glass appearance). There is usually an added pneumonic element and often the collapsed lung organizes. As the above autopsy demonstrated, there is an extension of caseation and a new growth of fibroblasts and capillaries throughout the lung. Such lungs soon become quite incapable of re-expansion, and thus, in assessing a lung's chances of recuperation after empyema onset, the extent of disease before it was collapsed must be considered.

Surgical treatment: Most operative procedures for tuberculous empyema are undertaken when conservative methods of treatment have had an extended trial, often over many months or even years, and have failed. A minority of surgeons operate on tuberculous empyema within a few weeks of its onset. It is proposed to discuss the two views.

In the series of cases of tuberculous empyema in the present review, 15 cases, all of the long-standing variety, were treated by surgical measures (table 6).

Of the 15 patients treated by operation, there were 8 deaths (53.3 per cent); the average duration of empyema in these cases was 57.4 months. There was full recovery without sinus in the chest wall in 4 of the patients (B, C, H, L), 26.7 per cent. In one patient (D), the general condition improved but the sinus persisted. In 2 patients (M, J), the sinus persisted and the general condition was deteriorating on April 3, 1948.

Thus good results with surgery were obtained in 5 patients and therapeutic failure or death occurred in 10 patients. This is an improvement over the results

with conservative treatment alone (table 5) where the deaths or impending deaths are 82.2 per cent and the cases with recovery only 17.8 per cent of the total. Those results compare with the series of cases treated surgically by Ornstein and Herman (1946) who had 34 per cent cured and 46.5 per cent deaths. Klassen, Miller, and Curtis (1946) found that only 38 per cent of their thoracoplasty cases were completely well but 50 per cent more were well except for a residual sinus.

TABLE 6

Tuberculous Empyema Treated Surgically

OPERATION CASE NUMBER	DURATION OF EMPYEMA BEFORE OPERATION	TOTAL EMPYEMA DURATION BEFORE RECOVERY OR DEATH	RESULT AND OUTLOOK
	months	*months*	
A	36	44	Death
B	15	144	Full recovery
C	48	108	Recovery
D	60	108	Persisting sinus on April 3, 1948; otherwise well and in good general condition.
E	5	13	Death; marked contralateral spread of disease after operation and persisting empyema
F	48	108	Death
G	114	132	Death
H	60	72	General condition only fair; probable closure of space on April 3, 1948
I	36	46	Death
J	32	73	Outlook bad; on April 3, 1948 has sinus and residual empyema; edema of legs and albuminuria
K	10	16	Death
L	6	26	Recovery
M	44	52	On April 3, 1948 patient deteriorating; outlook bad; empyema persists with sinuses
N	10.5	63	Death
O	20	37	Death

The operative procedures adopted for the patients listed in table 6 consisted of extensive thoracoplasties often with five and six stages. As a rule the residual empyema space, which is commonly present in the paravertebral gutter, had to be attacked by further plastic operation, as described be Estlander, Schede, or Roberts, or by the use of extensive muscle flaps. All operations on chronic tuberculous empyemata are made technically difficult by greatly thickened parietal and visceral pleura, the "tiling" of ribs, and fibrosis in the intercostal spaces. The decortication methods of Delorme and Fowler were not tried in this series nor were the modern operations whereby the lung and empyema are removed in toto in the endothoracic fascial plane.

Surgical measures for the control of tuberculous empyema can only be undertaken if the state of the opposite lung will permit and if the general condition of the patient will allow operative interference. The operation may have to be abandoned after any one stage because of flare-up of disease in the opposite lung or because of a bronchogenic spread through a fistula, if there has been no intubation prior to operation or inadequate aspiration between the stages. Again the successive severe stages of the operation leave their mark on some patients who either refuse to go on to the end of the program or are otherwise in too poor a condition for its completion.

In the series of cases under review it was possible from the roentgenograms and the clinical records to assess the condition in the opposite lung at the time of onset of empyema in 78 of the patients who did not have operative treatment.

In 54 cases, operative treatment was precluded from the start owing to contralateral disease. In 17 cases this took the form of "soft mottling" while in 35 cases there was cavitation as well. Two patients had an artificial pneumothorax present with airless lobe and no definite cavity. The contralateral lung was clear and considered safe for surgical interference on the empyema side in 24 cases. In 5 of the cases, however, there was doubt about the stability of "mottling" which was present and in another case there was marked, contralateral spread of disease four months after the first roentgenogram.

Therefore, in spite of our best intentions, a large percentage of patients with tuberculous empyema (58 per cent), when the 15 patients who had operation are included, are unfit for any but conservative treatment owing to contralateral disease. Knowing the bad results with conservative treatment, this figure envisages a poor over-all recovery rate from the outset, in spite of the best surgical efforts, when we are dealing with a hospital population in the R.B. 2 and R.B. 3 groups. In the ideal state of affairs, when empyemas follow on artificial pneumothoraces induced for unilateral disease, a larger proportion of cases would be fit for surgery.

The great majority of patients operated on for long-standing tuberculous empyema end with a residual empyema space or a persistent sinus. There is no doubt that many are improved after operation even with a small residual space, because they are relatively better off by virtue of a diminution in the large pleural surface from which septic absorption formerly took place. On the other hand, we all know of many such patients who linger on, often with external sinuses, malodorous, and necessitating daily dressings, and who succumb to slow toxemia in the end.

The poor results with conservative treatment and with surgery in long-standing cases of tuberculous empyema compel us to consider early surgical treatment for which there are very strong grounds.

In many patients a spread of the disease to the opposite, healthy lung occurs during the long period of futile conservative treatment. As a consequence, these patients lose the only hope they had of surgical therapy. In many instances, thoracoplasty can be performed for a persistent nonpurulent effusion of the pleural space of that side and, provided judicious aspiration is performed between

stages, the patients may do very well. The condition of the pleura is less thick in this situation than in the case of purulent effusions and corresponds to the state of affairs that would be present if early surgery was undertaken in empyema cases.

With gas analysis it is possible to ascertain the approximate size of the bronchopleural fistula present. Only in the case of the smallest fistula is it justifiable to try vigorous conservative methods of treatment and even the presence of a punctiform or a healed fistula is no guarantee that the lung will come out because, if the parenchymal disease is extensive, rapid pneumonitis and carnification may ensue. In the case of a larger fistula it is logical that delay will gain nothing. Instead it will further thicken the pleura and tend to cause chest wall sinuses, secondary infection, and a progressive deterioration in the patient's general condition. If the contralateral lung is slightly involved and there is doubt about the advisability of operating, there is now a more hopeful outlook because streptomycin can be used before, during, and after the operation.

After three months of conservative treatment very few lungs, if not expanded, finally re-expand because of pleural thickening. It is this same thickening which leads to the poor results with surgery after that period. Early surgical treatment, therefore, appears to be a logical recommendation. Finally, the results, such as those obtained by Brock (1943), prove that the use of early surgery should be given wider consideration, i. e., "surgery measured in days, not weeks and certainly not in months." Smyth (1947) quotes Archibald as believing that thoracoplasty should be done if the patient is not well on the way to recovery in one to three weeks with aspiration and lavage.

For the surgeon to be able to operate early entails close cooperation or team work with the physician, as prevails in thoracic surgical centers. The trouble arises where artificial pneumothorax is conducted in smaller institutions with no surgical staff, and it is necessary for those workers in the field to realize the urgency of the condition and to enlist the surgeon's help as soon as the empyema develops. It is believed, from a close personal study of the problem, that six to eight weeks is the maximum one should wait. If the lung has not completely reexpanded, then, and no later, should surgery be urged. This allows for a delay of two weeks at the least for a review of the films, arranging for a bed on the surgical service, and a place on the operating list, and it enables the patient to have the operation when his empyema has lasted just less than three months. Surgery after the three-month period is bound to have the same results as in long-standing cases of empyema.

SUMMARY

One hundred forty-six cases of tuberculous empyema among 7,206 cases of pulmonary tuberculosis treated at the Baguley Sanatorium have been reviewed. The management of tuberculous empyema and its mortality are analyzed from the standpoint of surgical or nonsurgical therapy.

It is believed that tuberculous empyema should be treated by surgical therapy at a very early stage in its course.

SUMARIO

Empiema Tuberculoso: Evolución Clínica y Asistencia

Después de definir el empiema, enuméranse las causas en 146 casos. Señálase la relación del derrame estéril con el neumotórax terapéutico.

Trázase una comparación entre los empiemas tuberculosos puros y los de infección mixta y enuméranse los varios microbios descubiertos en 25 casos de los últimos.

Después de una reseña de la evolución clínica del empiema tuberculoso, consígnase la mortalidad global en 105 casos, independientemente de la forma de tratamiento usado.

Bajo los encabezados de tratamiento conservador y cirugía, descríbense la asistencia del estado y la mortalidad en casos prolongados.

Menciónanse las razones por las que debe emprenderse la cirugía en una etapa muy temprana de la evolución del empiema.

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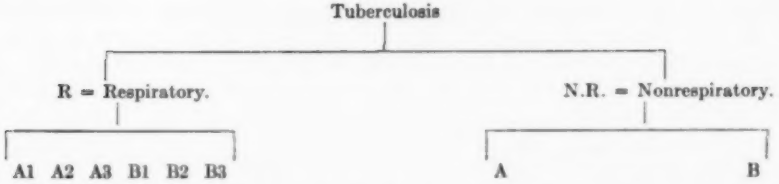
Appendix

CLASSIFICATION



CLASS A: Cases in which tubercle bacilli have never been discovered in any exudate, excrement, discharge, or tissue.

CLASS B: Cases in which tubercle bacilli have been found at any time in any exudate, excrement, discharge, or tissue.

Group 1. Cases with slight constitutional disturbance, if any, e.g., there should not be marked acceleration of pulse or elevation of temperature except of very transient duration; gastrointestinal disturbance or emaciation, if present, should not be excessive. Obvious physical signs and radiological findings should be of very limited extent. The physical signs should be either present in one lobe only; and, in the case of an apical lesion of one upper lobe, not extending below the second rib in front, or not exceeding an equivalent area in any one lobe; or, where these physical signs are present in more than one lobe, they should be limited to the apices of the upper lobes, and should not extend below the clavicle and the spine of the scapula.

Radiological findings should be limited to mottling involving a total area of not more than one zone.

No complications (tuberculous or other) of prognostic gravity should be present. A small area of dry pleurisy should not exclude a case from this group.

Group 3. Cases with profound systemic disturbance or constitutional deterioration and with marked impairment of function, either local or general.

All cases with grave complications, whether they are tuberculous or not, should be classified in this group (diabetes, tuberculosis of intestine or larynx).

Group 2. All cases which cannot be placed in groups 1 and 3.

AIR EVACUATION OF TUBERCULOUS MILITARY PATIENTS[1,2]

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INTRODUCTION

The potential immediate hazards of air travel for tuberculous patients, particularly those with pneumothorax, have been discussed in the literature (1–9) but, in general, only the known or probable manifestations occurring in or immediately after flight are considered. An additional article by Barach, *et al.* (10) is interesting but deals with factors which obtain at much higher altitudes than are flown by nonpressurized airplanes.

There has been no other known study of subsequent clinical developments in a sizable series of tuberculous patients who have traveled relatively long distances by airplane, or even a full evaluation of the possible effects on the patients' toxemia. Does this mode of travel cause harm to the patient and his disease during or immediately after flight? If immediate ill effect occurs, does it lead to long-range worsening of disease? Does flying produce eventual harm at some later date, not evidenced or suggested by untoward reaction in or immediately following flight?

This report is concerned with the immediate and long-range effects of transportation by airplane of 143 military patients having active pulmonary parenchymal tuberculosis in various stages. It is based on a survey initiated in the fall of 1944 as a side mission of the Section for Research on Minimal Tuberculosis. At the time of this study, air-ambulance-planes were not equipped for cabin pressurization at higher altitudes, a desirable feature which has become generally available in more recent years.

Air travel entails high speeds and occasional jolting of the entire body. In nonpressurized airplanes, it also involves sharp changes of altitude, barometric pressure, and oxygen tension, any or all of which might affect the course of a chronic infectious disease of the lungs. The present study deals only with the immediate and eventual reactions to the composite of these factors; it is not concerned with an effort to analyze the potential differential influences of the physical and physiologic components involved.

PLAN OF INVESTIGATION

In an effort to eliminate some of the known variables, such as age, sex, and race, the series was restricted to white males, 22 to 28 years of age. Prior to

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evacuation by air, each of the 143 patients had been diagnosed as having active pulmonary tuberculosis, confirmed in practically all instances by sputum or gastric washings positive for *M. tuberculosis*, and had been observed in a distant hospital for at least two weeks. Each had been in flight for eight hours or more. The series was established to include all airborne patients who fulfilled these basic requirements and who arrived at Hamilton Field, Fitzsimons General Hospital, or Bruns General Hospital during the periods devoted to the study. At initial pre-flight diagnosis, the disease had been *minimal* in 59 instances, *moderately advanced* in 56, and *far advanced* in 28, according to the classification standards of the National Tuberculosis Association.

Each case study was initiated by preliminary direct observation on arrival via air ambulance, followed by full interview within a day or two after deplaning. With very rare exceptions, the air-borne evacuée exhibits less fatigue, less anxiety, more cheerfulness, and higher morale than does the patient who has traveled by train or boat. This statement is substantiated by similar direct observations on hundreds of tuberculous patients arriving via boat or train. Rapidity of safe return home, or transfer to the designated place of definitive treatment, obviously is desired by all.

Details regarding selection of cases for evacuation by airplane, symptoms and objective reactions in flight, duration and maximum altitude of flight, roughness of travel, et cetera,[1] were checked with the medical officers, nurses, and medical corpsmen who accompanied the patients and with the flight crews concerned. Patients with pre-existing therapeutic or spontaneous pneumothorax were not transported by air, nor were the ones with large cavities and associated toxemia. In this group and also among several hundred other tuberculous air evacuées seen more casually by us, there was no occurrence of spontaneous pneumothorax during or following flight. On the other hand, spontaneous pneumothorax has developed several times among other tuberculous patients being transferred by train to Denver, Colorado, and more often in those crossing Raton Pass by train enroute to Santa Fe, New Mexico.

In a very few instances of minimal disease without clinical toxemia, the patients were transferred on an ambulatory status. All others were handled as litter cases, remaining recumbent throughout flight. The "sitter" cases fared no better and no worse than the ones in litters, with regard to flight symptoms, post-flight toxemia, or subsequent course of disease. Less than one-half of the group had flown in airplanes previously.

OBSERVATIONS

Flight Data and Symptoms in Flight

Total duration of flight or of consecutive related flights ranged from eight hours in some instances to fifty-odd in a few, with a mean of approximately twenty hours. Military patient flights do not extend longer than eight hours at a time except for transoceanic or emergency hops. There was no correlation whatsoever between duration of flight and (*1*) aggravation of symptoms during flight, (*2*) increase in toxemia immediately thereafter, or (*3*) subsequent course of disease.

In evacuating patients via nonpressurized airplanes, the policy is to fly at 8,000 feet or lower whenever possible, but higher altitudes prove necessary on occasion because of storms at lower levels or mountainous terrain such as forms the approaches to Fitzsimons and Bruns General Hospitals. The maximum altitudes attained by the patients in the series were: 8,000 feet or less, 11 patients; from 8,000 and up to 10,000 feet, 61 patients; and more than 10,000 feet, 71 patients, of whom 14 reached 15,000 feet or higher at some time during their flights.

Throughout the study, the recorded maximum altitude represents the highest above sea level for thirty minutes or more. Although it is admitted that higher altitudes might have been reached briefly, no such instances were reported or recorded. Altitudes above 10,000 feet were not maintained for more than two hours in any case, and rarely for more than one hour.

Seventeen of the 143 patients experienced discomfort, which they and the writers attributed to the conditions of air travel, for a total of twenty complaints (table 1). Neither frank pulmonary hemorrhage nor spontaneous pneumothorax occurred in any instance during or following flight. Dyspnea was not

TABLE 1

Flight Symptoms

Dyspnea	6	Increase of fatigue	1
Blood-streaked sputum	3	Cold, lack of sleep	1
Nervousness	3	Pleural pain	1
Head congestion	2	Nausea	1
General discomfort	2		

Total: 20 symptoms in 17 patients

severe or prolonged in any of the 6 occurrences. Each of the patients claimed that he fared as well as his nontuberculous fellow passengers. All but one indicated a decided preference for travel by air rather than boat or train. Moreover, the last-named patient's only symptom was nervousness for which he had been hospitalized prior to recognition of his minimal tuberculosis.

In nonpressurized airplanes, oxygen is offered routinely to all patients at altitudes of 10,000 feet or higher, and to those having pulmonary disease at lower levels of 6,000 to 7,000 feet. Only a few of the 143 actually inhaled the oxygen, however; up to 12,000 to 14,000 feet, they "felt comfortable without it."

The occurrence of symptoms was not affected significantly by the presence or absence of cavitary disease (table 2, A). In each group, symptoms were absent to rare at altitudes of 10,000 feet or less and were more frequent above 10,000 feet, occurring in approximately 20 per cent of both those with and those without demonstrable cavities. The pre-flight cavities ranged in size from "honeycombing" in some cases to total diameters of 8 cm. in two, with a mean of about 4 cm. The patients with larger cavities exhibited essentially the same flight reactions as did those with smaller ones. Data regarding sizes of cavities

TABLE 2

Symptoms during Flight

PRE-FLIGHT DISEASE	MAXIMUM ALTITUDE	FLIGHT SYMPTOMS				
		None	Mild	Moderate	Total	
	feet					
A.						
Noncavitary, 73	10,000 or less	35	3	0	38	
	10,000+	28	7	0	35	
						73
Cavitary, 70	10,000 or less	34	0	0	34	
	10,000+	29	6	1	36	
						70
	Total	126	16	1		143
B.						
Minimal, 59	10,000 or less	29	2	0	31	
	10,000+	22	6	0	28	
						59
Moderate, 56	10,000 or less	31	1	0	32	
	10,000+	20	4	0	24	
						56
Far advanced, 28	10,000 or less	9	0	0	9	
	10,000+	15	3	1	19	
						28
	Total	126	16	1		143
	Recapitulation					
C.	10,000 or less	69	3	0	72	
	10,000+ to 14,000+	46	11	0	57	
	15,000 or more	11	2	1	14	
	Total	126	16	1	143	

by roentgenographic examination *during* flight are not available; there was no instance of prominent "blowing-up" of cavity immediately after air travel.

Regardless of the stage of pre-flight disease, the occurrence of symptoms at 10,000 feet and less was low (table 2, B). At altitudes above 10,000 feet, symp-

toms developed in 6, or 21.4 per cent, of the 28 minimal cases; in 4, or 16.7 per cent, of the 24 moderately advanced, and in 4, or 21.1 per cent, of the 19 patients with far advanced disease.

In recapitulation (table 2, C), symptoms developed in 3, or 4.2 per cent, of the 72 patients flown at 10,000 feet or less; in 11, or 19.3 per cent, of the 57 at between 10,000 and 15,000 feet; and in 3, or 21.4 per cent, of the 14 who went to 15,000 feet and higher. Combining the figures for the 71 who exceeded 10,000 feet, symptoms occurred in 14, or 19.7 per cent. (In all *detailed* tables and discussions, the 14 who attained maximum altitudes of 15,000 feet and higher are included with those recorded as "exceeded 10,000 feet." With larger figures, in each of the more gross recapitulations, they are shown as a separate segment.)

TABLE 3

Classification of Toxemia for Airborne Patients

	A. NONE	B. MODERATE	C. SEVERE
Symptoms	None	Mild–moderate	Moderate–severe
Temperature & pulse rate	Normal	Normal–slightly elevated	Elevated
Abnormal physical signs, chest	None–minimal	None–moderate	None–extensive
General condition of patient	Excellent–good	Good–fair	Fair–poor
Laboratory:			
Erythrocyte sedimentation rate	Normal	Normal–slightly elevated	Normal–elevated
WBC, total and differential	Normal	Normal–slightly elevated	Normal–elevated
Sputum/gastric washings	Negative or positive	Negative or positive	Positive

Pre-flight and Post-flight Toxemia

For this study, a classification proved necessary and was formulated arbitrarily as a guide to grading the patients according to absence or degree of toxemia (table 3). Fever and malaise are considered generally as the primary symptoms of toxemia in tuberculous patients. In their absence, other evidence becomes more significant in evaluating toxemia.

Wide discrepancies between the listed factors (table 3) and contemporaneous chest roentgenographic findings are known to occur in many patients with tuberculosis, partially as a result of a delay or a lag period between the appearance of changes detectable clinically and by roentgenographic examination. The classification of general clinical condition or degree of toxemia employed herein does not include reference to the extent or nature of abnormalities detectable on the roentgenogram. Nevertheless, consideration of roentgenographic changes plays a prominent role in evaluation of the long-range course of disease, as discussed below.

Toxemia prior to flight was absent in 45 patients, moderate in 76, and severe

TABLE 4

Pre-flight Data

STAGE OF DISEASE	TOXEMIA			TOTAL
	None	Moderate	Severe	
Minimal	42	17	0	59
Moderately advanced	3	45	8	56
Far advanced	0	14	14	28
Total	45	76	22	143

TABLE 5

*Post-flight Toxemia**

	MAXIMUM ALTITUDE 10,000 FEET OR LESS			MAXIMUM ALTITUDE EXCEEDED 10,000 FEET			
	Post-flight toxemia			Post-flight toxemia			
	Unchanged	Less	More	Unchanged	Less	More	Total
A. Pre-flight disease							
Noncavitary, 73	27	9	2	26	9	0	73
Cavitary, 70	13	20	1	20	16	0	70
Total	40	29	3	46	25	0	143
B. Pre-flight toxemia							
None, 45	21	0	2	22	0	0	45
Moderate, 76	19	20	1	22	14	0	76
Severe, 22	0	9	0	2	11	0	22
Total	40	29	3	46	25	0	143

C. Recapitulation

MAXIMUM ALTITUDE	POST-FLIGHT TOXEMIA			
	Unchanged	Less	More	Total
Feet				
10,000 or less	40	29	3	72
10,000+ to 14,000+	36	21	0	57
15,000 or more	10	4	0	14
Total	86	54	3	143

* See table 3: "Classification of Toxemia for Airborne Patients."

in 22 (table 4). As expected, toxemia was evident more frequently in the patients with more advanced disease.

In table 5, toxemia in the two weeks following flight is compared with that of the equivalent period preceding air travel. Obviously, if toxemia had been

absent before, it could not decrease afterwards; any *change* which occurred would have to be reflected as an increase. Similarly, change in a pre-flight grade of severe toxicity could be represented only as less.

Toxemia increased immediately following air evacuation in only 3 of the 143 patients. Two of these had been nontoxemic prior to flight, and one moderately so (table 5, B); 2 had noncavitary disease and one, disease with cavitation (table 5, A). None of the 3 flew higher than 10,000 feet. Toxemia in the cavitary group was not affected differently than in those without cavities. There was only one instance of increased toxemia among the 70 patients with cavities, 36 improved promptly, and 33 did not change. In the 73 patients with noncavitary disease, toxemia increased in 2, diminished in 18, and remained unchanged in 53 (of whom 43 had been nontoxemic originally).

Toxemia decreased promptly in 54 patients, of whom 34 previously had had a moderate degree and 20 a severe degree of such symptoms (table 5, B). Toxemia remained unchanged in 86 patients, including 43 with pre-flight grades of none, 41 classified as moderate, and 2 as severe.

Of the 22 patients with severe toxemia prior to air travel, the general clinical status improved promptly in 20. Eleven, or 50 per cent, of this particular group had exceeded 10,000 feet of altitude for periods of at least one-half hour and usually longer.

In recapitulation (table 5, C), toxemia decreased in 29 of the 72 patients who were flown at 10,000 feet or less, increased in 3 at these altitudes, and showed no change in 40. Above 10,000 and below 15,000 feet, there was no instance of increase, 21 of the 57 improved, and 36 continued in their pre-flight grades. Of the 14 who exceeded 15,000 feet, toxemia lessened promptly in 4 and remained stable in 10.

Subsequent Course of Disease

Follow-up observations have been conducted for thirty-six months or longer after flight by air ambulance in all of the 139 patients who lived beyond that period and for forty-eight or more months in 80 patients (table 6). These long-range observations have included repeated chest films and analyses of clinical records and laboratory findings. In most instances, the living patients have been re-examined personally by one of the writers (WHR) at least once during the follow-up period. All chest roentgenograms have been reviewed by the writers.

All of the 143 patients have undergone various periods of bed rest. In addition, operative procedures have been completed on 47 of the group as follows:

	Number of patients
Therapeutic pneumothorax	36
Thoracoplasty	7
Pneumoperitoneum with phrenemphraxis	4
Total	47

As mentioned previously, 84 of the total series had had moderately to far advanced disease before flight. The frequency of operative therapy in this series

closely approximates that for comparable groups of tuberculous military personnel evacuated by surface transportation to Fitzsimons or Bruns General Hospitals.

Four of the 143 patients have died, 2 with progressive tuberculosis and 2 of other causes (table 6). In each of the latter 2 instances, the tuberculous disease had improved steadily up to death. Of the 2 whose deaths were attributable to tuberculosis, one had flown at 11,000 feet and the other had not exceeded 8,000 feet; one died seven months following air evacuation and the other twenty-seven months after the flight.

In table 7 may be seen the subsequent course of tuberculosis in correlation with pre-flight disease and toxemia, with separation according to altitude. The long-range behavior of the disease is classified as *favorable*, indicating prompt

TABLE 6

Post-flight Observation Periods

	NUMBER OF PATIENTS	INCLUDING DECEASED
Less than 12 months	1	1 far advanced tuberculosis
12 to 23+ months	2	1 malaria; tuberculosis improving 1 homicide; tuberculosis improving
24 to 35+ months	1	1 far advanced tuberculosis
		4 Total
36 to 47+ months	59	
48 or more months	80	
Total	143	

and satisfactory regression, or as *unfavorable*, signifying repeated exacerbations or uninterrupted progression.

Noncavitary disease improved promptly in 35, or 92.1 per cent, and increased in 3, or 7.9 per cent, of the 38 patients who had flown at 10,000 feet or less (table 7, A); above 10,000 feet, noncavitary disease improved in 28, or 80 per cent, of the 35 patients concerned and worsened in 7, or 20 per cent. Among the 34 cavitary patients flown at the lower altitude levels, 33, or 97 per cent, improved and the disease became worse in one. Thirty-six patients with cavities exceeded 10,000 feet, of whom 32, or 88.9 per cent, responded favorably to subsequent treatment and 4, or 11.1 per cent, did not fare as well as desired.

Pre-flight stage of disease is shown in table 7, B, with subsequent long-range developments after flight. In the minimal group, the patients who exceeded 10,000 feet have not done quite as well as those flown at lower altitudes. To less degree, the same applies to the moderately advanced and far advanced cases.

In each of the altitude groups, statistical tests have been made with regard to

possible correlation between long-range clinical course and (*1*) pre-flight toxemia (table 7, C), or (*2*) change in degree of toxemia following flight. Significant relationship was not found.

TABLE 7

Subsequent Clinical Course

	MAXIMUM ATTITUDE 10,000 FEET OR LESS		MAXIMUM ALTITUDE EXCEEDED 10,000 FEET		
	Clinical course		Clinical course		
	Favorable	Unfavorable	Favorable	Unfavorable	Total
A. Pre-flight disease					
Noncavitary, 73	35	3	28	7	73
Cavitary, 70	33	1	32	4	70
Total	68	4	60	11	143
B. Pre-flight disease					
Minimal, 59	28	3	21	7	59
Moderate, 56	31	1	22	2	56
Far advanced, 28	9	0	17	2	28
Total	68	4	60	11	143
C. Pre-flight toxemia					
None, 45	20	3	19	3	45
Moderate, 76	39	1	29	7	76
Severe, 22	9	0	12	1	22
Total	68	4	60	11	143

D. Recapitulation: Subsequent clinical course

MAXIMUM ALTITUDE	FAVORABLE	UNFAVORABLE	TOTAL
feet			
10,000 or less	68	4	72
10,000+ to 14,000+	49	8	57
15,000 or more	11	3	14
Total	128	15	143

Recapitulating without regard to other factors (table 7, D), the subsequent course of disease among the 72 patients who flew at 10,000 feet or less has been favorable in 68, or 94.4 per cent, and unfavorable in 4, or 5.6 per cent. Of 57 whose flight-altitudes were between 10,000 and 15,000 feet, 49, or 86 per cent, have improved and 8, or 14 per cent, have not fared so well. In the smaller group

of 14 evacuées who reached or exceeded 15,000 feet, 11, or 78.6 per cent, have handled their disease satisfactorily and 3, or 21.4 per cent, have regressed or relapsed.

In summation, without consideration of any other factors, long-range follow-up of the clinical course of tuberculosis among 143 military air evacuées has revealed:

1. Regression of disease, general improvement, favorable response to therapy in 128 patients, or 89.5 per cent of the total series.
2. Progressive increase or repeated relapses, failure of improvement, unfavorable response to treatment in 15, or 10.5 per cent of the patients.

No attempt was made to establish parallel series of "control cases" evacuated by surface transportation. The behavior of tuberculosis varies so widely in different individuals, even of the same ages and races, that a much larger number of case studies in each category would have to be completed before direct statistical comparisons could be dependable. On the basis of general medical experience, however, and particularly from unrecorded observations on hundreds of boat-borne, train-borne, and other air-borne tuberculous soldier patients, it is believed that the over-all course of tuberculosis in these 143 airborne patients compares quite favorably with any similar group transported by other means.

SUMMARY

In 143 soldier patients with active pulmonary tuberculosis, in all stages of involvement, a study has been made immediately after travel in nonpressurized air ambulances and for three or more years thereafter. All were white males, ranging in age from 22 to 28 years.

Severe discomfort, pulmonary hemorrhage, and spontaneous pneumothorax did not occur in the series either during or following flight. Evidences of toxemia appeared or increased immediately after flight in only 3 patients.

The subsequent long-range course of disease was favorable in 128, or 89.5 per cent, and unfavorable in 15, or 10.5 per cent, of the series. Of the 15 patients whose disease worsened at some time during post-flight observation, 4 had been flown at 10,000 feet or less, representing 5.6 per cent of the 72 in the lower altitude group; 11 had exceeded 10,000 feet, representing 14.1 per cent of the 71 who attained higher altitudes in nonpressurized airplanes.

CONCLUSIONS

1. Almost all military tuberculous patients have expressed a decided preference for transportation by airplane rather than by boat or train.

2. In the absence of contraindications such as very severe toxemia, large cavities, extensive loss of air-bearing lung tissue, or pneumothorax, air travel appears to be safe for tuberculous patients at altitudes up to 10,000 feet, and even preferable to slower modes of transportation.

3. The ultimate influence of flight altitudes above 10,000 feet is difficult to appraise. The experiences of this survey suggest, however, that the eventual

course of disease is not as favorable among patients who exceed 10,000 feet in nonpressurized airplanes as among those who are flown at levels below 10,000 feet.

SUMMARIO

Evacuación Aérea de los Militares Tuberculosos

Este estudio comprendió 143 soldados que tenían tuberculosis pulmonar en varias fases de desarrollo, inmediatamente después de haber viajado en ambulancias aéreas sin modificación de la presión interna y durante tres o más años subsiguientemente. Todos eran varones blancos, cuya edad variaba de 22 a 28 años.

No se observaron en la serie ni durante el vuelo ni después, malestar intenso, hemorragia pulmonar o neumotórax espontáneo. Sólo en 3 enfermos se presentó toxicidad (o aumentó la misma) inmediatamente después del vuelo.

La evolucion subsiguiente a plazo largo de la enfermedad fué favorable en 128, o sea 89.5 por ciento, y desfavorable en 15, o sea 10.5 por ciento, de la serie. De los 15 enfermos cuya afección empeoró en alguna ocasión durante la observación postvuelo, 4 habían volado a tres mil metros de altura o menos, representando 5.6 por ciento de los 72 en el grupo de menor altitud; y 11 habían excedido de tres mil metros, constituyendo 14.1 por ciento de los 71 que alcanzaron mayores alturas en aviones sin modificación de la presión interna.

Conclusiones

1. Prácticamente todos los militares tuberculosos han expresado decidida preferencia hacia el transporte por avión, más bien que por barco o tren.

2. En ausencia de contraindicaciones, tales como toxicidad muy grave, cavernas grandes, extensa pérdida de tejido pulmonar aerífero o neumotórax, el viaje por aire parece inocuo para los tuberculosos a alturas hasta de tres mil metros, y hasta preferible a medios más lentos de transporte.

3. Resulta difícil justipreciar el influjo final ejercido por los vuelos a elevaciones superiores a tres mil metros. Sin embargo, lo observado en este estudio indica elocuentemente que la evolución eventual de la dolencia no es tan favorable en los pacientes que pasan de tres mil metros en aviones sin modificaciones de la presión como en aquellos que viajan a menos de tres mil metros de altura.

Acknowledgments

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LABORATORY DIAGNOSIS OF PULMONARY MYCOSES[1,2,3]

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INTRODUCTION

Fungus infections of the lungs are subacute or chronic infections which notoriously simulate tuberculosis clinically and pathologically. Clinically, a benign primary infection caused by *Coccidioides immitis* or *Histoplasma capsulatum* may result in calcification and roentgenographic findings which are indistinguishable from primary tuberculosis. Also, an associated sensitivity to these fungi or their products (coccidioidin, histoplasmin) is established early in the disease and is retained for years. A malignant secondary progressive infection is known to occur in a small percentage of infections caused by these fungi in which a hematogenous spread results in metastasis to many organs of the body. As in fatal tuberculosis, anergy can be demonstrated in the moribund patient with resulting loss of sensitivity.

Pathologically, the lesions produced as a result of infection by fungi are typical granulomata and may be mistaken for those of tuberculosis grossly or microscopically unless the invading organisms are carefully identified. Since fungi produce subacute or chronic infections which mimic tuberculosis closely, an accurate diagnosis of such diseases must depend upon careful laboratory studies of materials obtained from patients. Such studies should include a direct microscopic examination of sputum, cultures of sputum, pathogenicity tests of organisms isolated, and sensitivity and serologic tests. The following fungi may cause pulmonary disease: *Actinomyces bovis*, *Nocardia asteroides*, *C. immitis*, *Blastomyces dermatitidis*, *B. brasiliensis*, *H. capsulatum*, *Cryptococcus neoformans*, *Candida albicans*, and *Geotrichum candidum*.

MICROSCOPIC EXAMINATION OF SPUTUM

Unstained (Fresh) Preparations

Sputum should be examined by placing a loopful on a microscope slide and covering the preparation with a cover glass. Occasionally, a loopful of tenacious or pus-laden sputum may be mixed on a slide with a drop of potassium hydroxide (10 per cent) for clearing, and examined under a cover glass after gently heating over a low flame of the bunsen burner. Also, the sediment of concentrated sputum should be examined if the organisms are thought to be too infrequent to be found in smaller amounts of the material.

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[2] Presented before the Southern Tuberculosis Conference, Memphis, Tennessee, on September 16, 1949.

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Microscopic examination of such preparations should be made with the low and high dry objectives of the microscope and with reduced light. It has been found, because of lack of contrast, that a brilliant light causes the fungus bodies to blend with the background and to be difficult to differentiate from other cellular materials. The tissue phase of many of the fungi, as found in the sputum, is distinctive enough to allow a provisional diagnosis. The following fungi may be detected in unstained preparations of sputum.

Actinomyces boris appears as an amorphous mass of material in the form of lobulated granules which may be seen macroscopically by placing the prepared slide on a dark background or by holding up the slide to a source of light. Microscopically, such granules are seen to be composed of a dense tangle of delicate mycelium one μ or less in diameter with or without the characteristic clubs at the periphery (plate I, figure 1). Since bacterial colonies may simulate an actinomycotic granule, stained preparations also should be made and examined (see below).

C. immitis appears as large, thick-walled spherules, 10 to 80 μ in diameter, with few to numerous endospores (plate I, figure 2). The smaller, immature nonendosporulating spherules are not distinctive enough for identification and a complete search of the preparation should be made for the mature forms.

B. dermatitidis appears as large, thick-walled, *single budding* yeast-like cells, 5 to 20 μ in diameter (plate I, figure 3). It may be necessary to examine several preparations, or the sediment of a concentrated specimen of sputum, because of the scarcity of organisms.

B. brasiliensis appears as large, thick-walled, *multiple budding* yeast-like cells 10 to 60 μ in diameter (plate I, figure 4). The great variation in size and tendency to multiple budding characterize this fungus. Smaller, single-budding forms, however, should not be mistaken for *B. dermatitidis*. So far, this fungus has been reported only from South America.

C. neoformans appears as large, thick-walled, single budding yeast-like cells 5 to 15 μ in diameter (plate I, figure 5). Although a halo seems to surround these cells, such an appearance may be thought to be due to refracted light. It would be difficult to distinguish this fungus from *B. dermatitidis* unless india ink preparations are made (see below).

C. albicans appears as small, oval, thin-walled yeast-like cells 2.5 by 4 to 6 μ with occasional fragments of pseudomycelium, 4 to 6 μ in diameter (plate I, figure 6). All species of *Candida* appear similar in sputum. Therefore, a specific identification must depend on cultural techniques.

G. candidum appears as rectangular elements, 4 to 6 by 8 to 12 μ in size (arthrospores) with occasional thick-walled rounded cells 8 to 15 μ in diameter (plate I, figure 7). Such rounded cells may be mistaken for *B. dermatitidis*. When there is a mixture of cells which includes arthrospores, however, *Geotrichum* should be suspected.

Stained Preparations

Although most fungi causing pulmonary infections may be detected in fresh preparations of sputum, some fungi are more easily detected in stained smears.

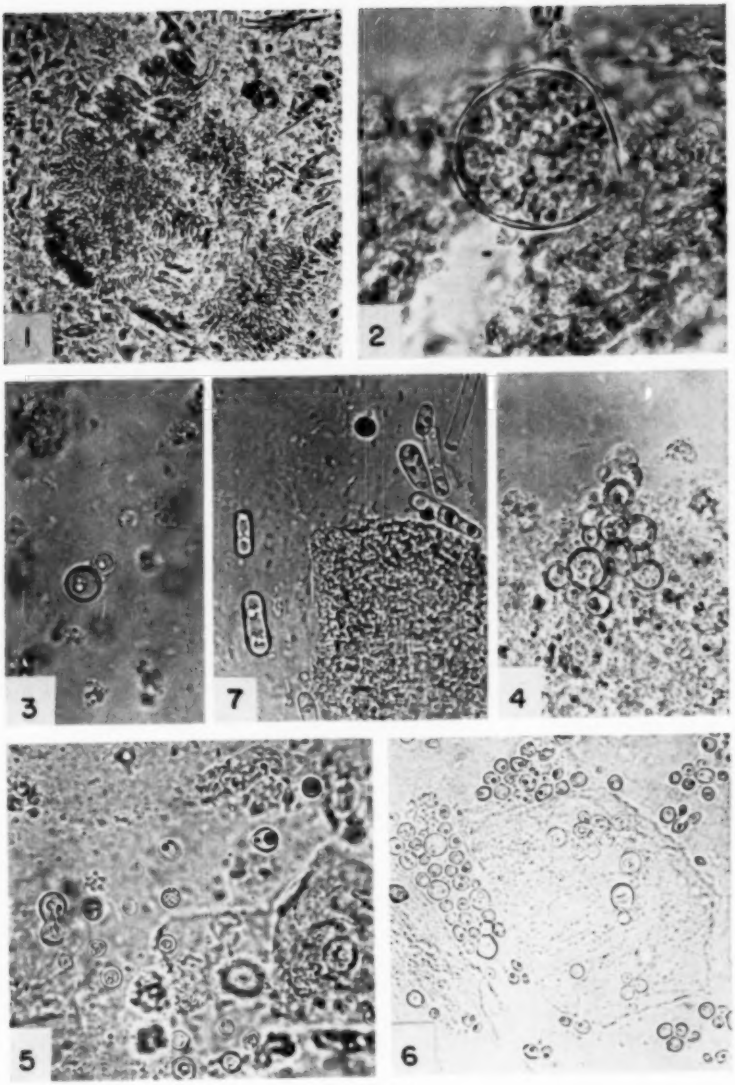

PLATE I

Fresh Preparation of Sputum

Fig. 1. *A. boris*; crushed granule with clubs. 850×.
Fig. 2. *C. immitis*; spherule with endospores. 790×.
Fig. 3. *B. dermatitidis*; thick-walled, single budding cell. 790×.
Fig. 4. *B. brasiliensis*; thick-walled, multiple budding cells. 790×.
Fig. 5. *C. neoformans*; thick-walled budding cells. 790×.
Fig. 6. *C. albicans*; thin-walled oval budding cells. 790×.
Fig. 7. *G. candidum*; rectangular cells. 790×.

Such fungi include *A. bovis*, *N. asteroides*, *C. albicans*, *G. candidum*, and *H. capsulatum*. Smears are prepared as for staining for *M. tuberculosis* and should be stained with Ziehl-Neelsen or Geimsa stains or by Gram's method.

A. bovis granules should be crushed under the cover glass or between two slides and thin smears prepared. Stained by Gram's method, the crushed granule is seen to be made up of gram-positive, delicate, bacillary, branching filaments (one μ in diameter) (plate II, figure 1). Such a preparation distinguishes the true actinomycotic granule from bacterial colonies which may appear in sputum.

N. asteroides appears as gram-positive or partially acid-fast, delicate, bacillary, branching filaments (one μ in diameter). In the absence of granules in fresh preparations, such stained smears should permit a provisional diagnosis.

C. albicans appears as gram-positive, small, oval, budding, yeast-like cells 2.5 by 4 to 6 μ with gram-positive constricted filaments to which budding spores may be attached (plate II, figure 2). Such forms are encountered frequently in acid-fast stained smears of sputum as deeply blue-stained yeast-like cells.

G. candidum appears as gram-positive, rectangular, or rounded cells 4 to 6 μ by 8 to 12 μ in size (plate II, figure 3). These cells also take the methylene blue counter stain in acid-fast stained preparations of sputum and may be distinguished readily.

H. capsulatum appears as small, intra- or extra-cellular, partially stained, oval bodies 2 to 4 μ in Geimsa-stained smears of sputum (plate II, figure 4). The small size, lack of mycelium, and phagocytosis of these forms should allow a provisional diagnosis of histoplasmosis.

India Ink Preparations

India ink preparations are used to demonstrate the capsule which surrounds the budding, yeast-like cells of *C. neoformans*. A loopful of sputum should be mixed with a drop of india ink and the wet preparation examined under a cover glass. *C. neoformans* appears as an encapsulated, round, thick-walled, budding yeast-like cell 5 to 15 μ in diameter (plate II, figure 5).

CULTURE OF SPUTUM

Several media have been described for the isolation of fungi from clinical materials such as sputum which are heavily contaminated with bacteria. In 1942, Kurung (9) used a dextrose yeast extract medium of high acidity (pH 4.0) to inhibit bacterial growth. From this medium transfers were made to Sabouraud's agar for identification. In 1945, Thompson (24) described the undesirable aspects of Sabouraud's medium with and without crystal violet. He used successfully a hormone blood agar (pH 7.0) to which he added 2 units of penicillin and 10 units of streptomycin per ml. of medium. This medium supported the growth of several pathogenic fungi and proved useful in isolating *C. immitis* from sputum in pure culture. A selective medium for *C. immitis* (1 per cent ammonium chloride, 1 per cent sodium acetate, 0.8 per cent tribasic potassium phosphate, 0.04 per cent cupric sulfate, and 2 per cent agar) was described also by Smith (20) in

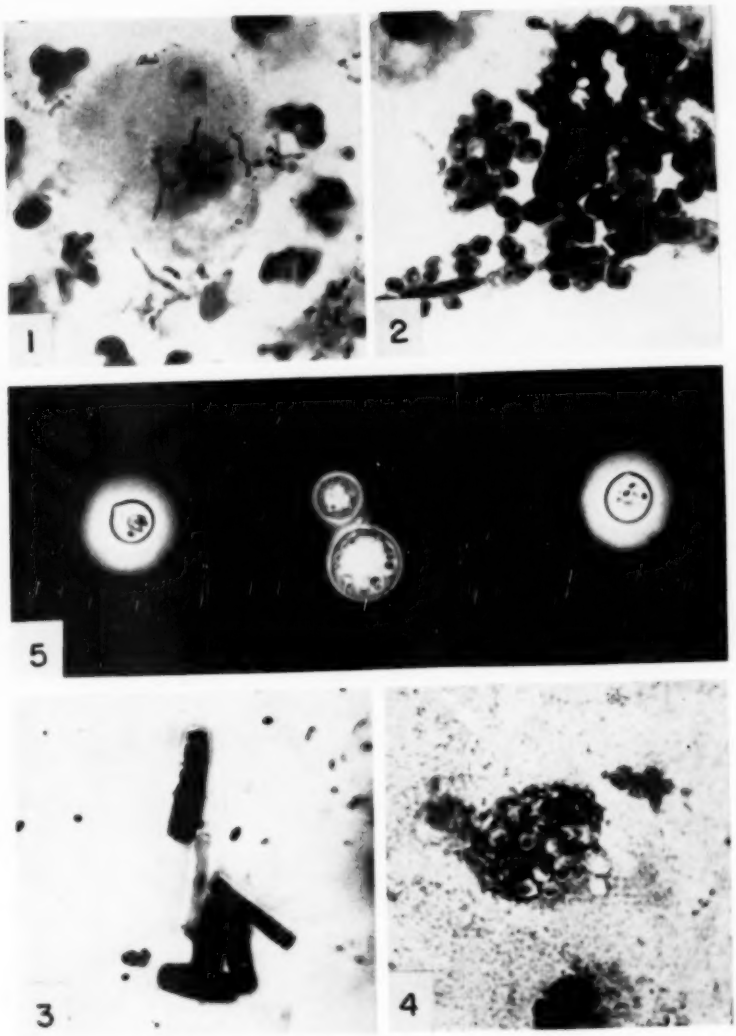

PLATE II

Stained Preparation of Sputum

FIG. 1. *A. bovis*; delicate gram-positive filaments. *N. asteroides* would appear similar but would also be acid-fast. 1775×.

FIG. 2. *C. albicans*; gram-positive oval budding cells and pseudohyphae. 1775×.

FIG. 3. *G. candidum*; gram-positive oblong cells, arthospores. 1775×.

FIG. 4. *H. capsulatum*; Geimsa-stained smear of sputum; oval cells in mononuclear cell. 1775×.

FIG. 5. *C. neoformans*; India ink preparation of sputum showing capsules. 1775×.

1943. In 1947 and 1948, Littman (10, 11) described an oxgall streptomycin crystal violet medium for the cultivation of fungi from contaminated clinical materials. This medium not only restricted bacterial growth but also restricted the size of fungus colonies. This latter is of advantage in that fast-growing fungus contaminants, i. e., *Aspergillus* et cetera, do not overgrow slow-growing pathogens. While this medium supported growth of most of the pathogenic fungi, *H. capsulatum* grew only after heavy inoculation. In 1948, Howell (8) used a brain-heart infusion blood agar with the addition of 20 units of penicillin and 40 units of streptomycin per ml. of medium for the successful cultivation of *H. capsulatum*.

While experience has shown that a medium containing penicillin and streptomycin (preferably a medium approaching neutrality) supports the growth of pathogenic fungi, there are two exceptions to be considered, i. e., *A. bovis* and *N. asteroides*. These fungi are susceptible to penicillin and streptomycin and must be cultivated on other media. Also, *A. bovis* is micro-aerophilic and special cultural techniques as described by Rosebury *et al.* (16) must be used. It should be emphasized that concentrated sputum should not be used when fungi are to be cultured as it is not known with certainty which, if any, of the fungi can withstand the various methods of concentration used.

Sputum containing *A. bovis* should be cultured on brain-heart infusion agar (pH 7.6) plates at 37°C. under 10 per cent carbon dioxide or in anaerobic jars with the addition of 5 per cent carbon dioxide. Smears should be made of small, yellowish colonies 1 to 3 mm. in diameter which appear in 3 to 6 days (plate III, figure 1). Such smears, if stained by Gram's method, should show delicate branching or diphtheroid gram-positive forms (plate III, figure 2). Also, deep shake tubes of beef infusion glucose agar or ground-meat medium may be used. In shake cultures growth becomes evident in 4 to 6 days as lobulated colonies concentrated in a band of growth 5 mm. wide about one cm. below the surface of the agar. Other colonies may be scattered through the depths of the agar column. Such colonies should be picked, smeared and stained, and examined for the typical microscopic morphology of *A. bovis*.

Sputum containing *N. asteroides* should be cultured on Sabouraud's glucose agar or beef infusion glucose agar (pH 7.4) at room temperature and at 37°C. The colonies developed in 7 to 14 days are rough, granular, and yellow to orange in color (plate III, figure 3). Prepared smears stained by Gram's method show gram-positive branching filaments (plate III, figure 4). This fungus also is partially acid-fast. Smears from cultures grown in milk medium best show this characteristic.

Sputum containing *C. neoformans* should be cultured on Sabouraud's glucose agar at room temperature and on beef infusion blood agar plus penicillin and streptomycin at 37°C. The colonies developed in 4 to 7 days are smooth, moist, mucoid, glistening and soft, or yeast-like (plate III, figure 5). Preparations for microscopic examination are made by emulsifying a portion of a colony in a drop of water. Such preparations show only budding, thick-walled, yeast-like cells (plate III, figure 6). India ink preparations, made by emulsifying a portion of a colony in a drop of india ink, reveal the characteristic capsule produced by *C. neoformans*.

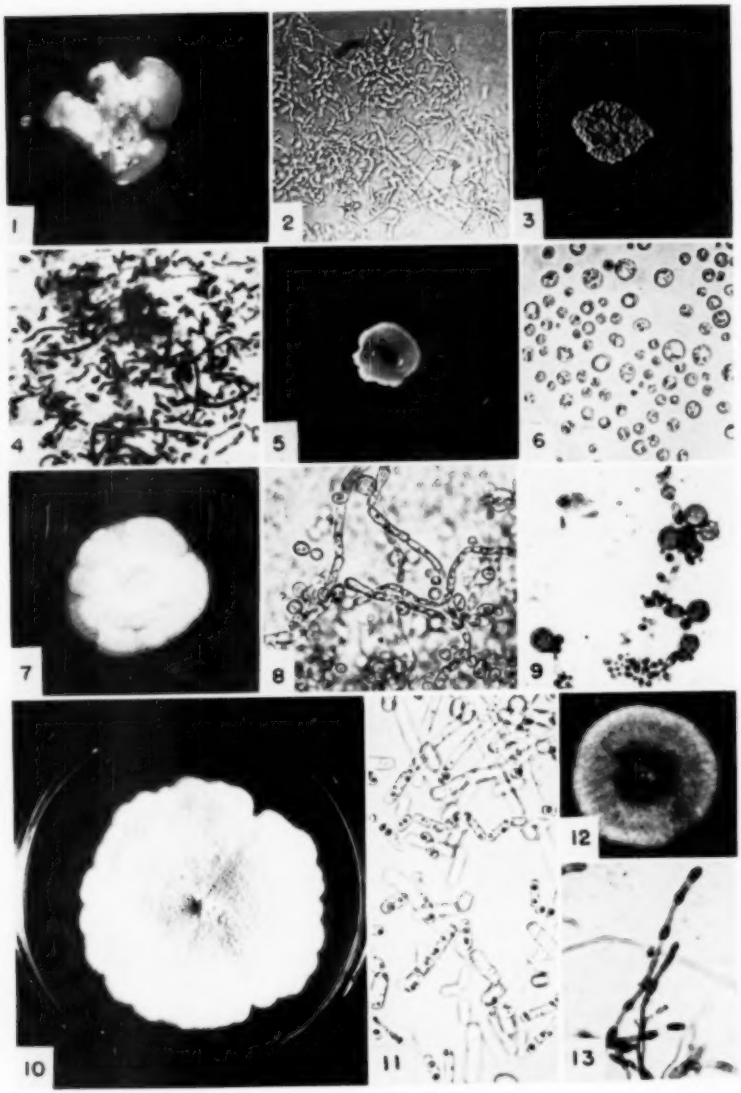

PLATE III

FIG. 1. *A. bovis* on brain-heart infusion glucose agar at 37°C. under 10 per cent carbon dioxide; 7 days. 10×.

FIG. 2. *A. bovis* from plate showing unstained preparation of delicate branching filaments. 850×.

Sputum containing *C. albicans* should be cultured on Sabouraud's glucose agar at room temperature and on beef infusion blood agar plus penicillin and streptomycin at 37°C. The colonies develope in 24 to 48 hours, have a yeasty odor, and are smooth, moist, dull white and soft, or yeast-like (plate III, figure 7). Preparations for microscopic examination are made by emulsifying a portion of a colony in a drop of water. Small, oval yeast-like cells are found in the surface growth; pseudomycelium will be found in the agar beneath the culture (plate III, figure 8). Typical and characteristic chlamydospores are produced best on corn meal agar at room temperature (plate III, figure 9). Species identification may be determined following the methods of Martin, *et al.* (14) and Martin and Jones (13).

Sputum containing *G. candidum* should be cultured on Sabouraud's glucose agar at room temperature and on beef infusion agar plus penicillin and streptomycin at 37°C. Colonies developed in 4 to 5 days are flat, mealy, and dry (plate III, figure 10). Preparations for microscopic examination should be made by emulsifying a portion of a colony in a drop of water. Such preparations reveal elongated, oblong arthrospores and wide septate hyphae (plate III, figure 11).

Sputum containing *C. immitis* should be cultured on Sabouraud's glucose agar at room temperature, the selective medium referred to above, and beef infusion glucose agar plus penicillin and streptomycin at 37°C. The colonies develop in 4 to 7 days as moist membranous growths which slowly become overgrown with white aerial mycelium; older cultures become buff to brown and powdery (plate III, figure 12). When making preparations for microscopic examination or when transferring cultures, every precaution should be made to prevent the powdery material from contaminating the air. This is a very infectious fungus and the culture should be wet (add sterile saline containing a drop of Tween 80) before manipulation. Petri dish cultures should not be used. Preparations for microscopic examination should be made in lactophenol cotton blue. Such preparations reveal arthrospore formation along the course of the hyphae with the deep-staining arthrospores separated by clear areas (plate III, figure 13). This type of spore formation is very typical of *C. immitis*.

Sputum containing *H. capsulatum* should be cultured on Sabouraud's glucose agar at room temperature and on brain-heart infusion blood agar plus penicillin and streptomycin at both room and incubator temperature. On Sabouraud's glucose agar, colonies develop in 7 to 14 days. They are slow growing with white

FIG. 3. *N. asteroides* on Sabouraud's glucose agar at room temperature; 21 days.
FIG. 4. *N. asteroides* from room temperature culture; gram-stained. 1775×.
FIG. 5. *C. neoformans* on Sabouraud's glucose agar at room temperature; 6 days.
FIG. 6. *C. neoformans* from Sabouraud's glucose agar. 750×.
FIG. 7. *C. albicans* on Sabouraud's glucose agar at room temperature; 18 days.
FIG. 8. *C. albicans* from Sabouraud's glucose agar. 790×.
FIG. 9. *C. albicans* showing chlamydospores from corn meal agar. 790×.
FIG. 10. *G. candidum* on Sabouraud's glucose agar at room temperature; 7 days.
FIG. 11. *G. candidum* from Sabouraud's glucose agar. 790×.
FIG. 12. *C. immitis* on Sabouraud's glucose agar at room temperature; 7 days.
FIG. 13. *C. immitis* from Sabouraud's glucose agar. 790×.

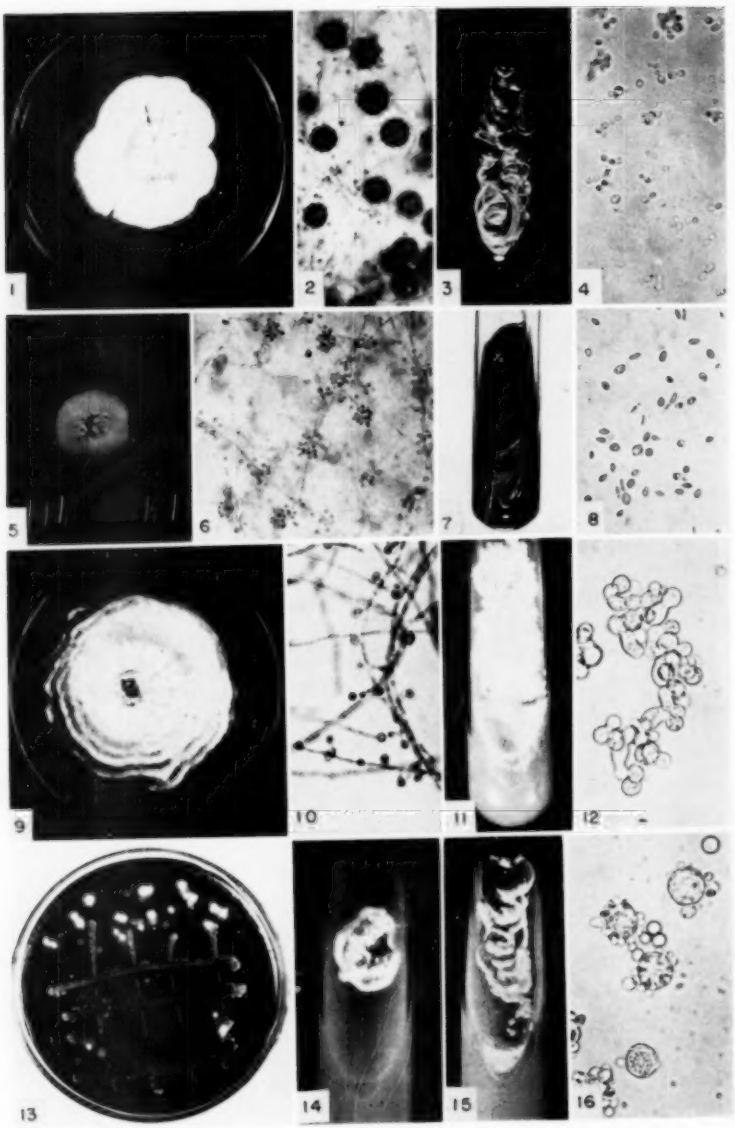

PLATE IV

FIG. 1. *H. capsulatum* on Sabouraud's glucose agar at room temperature; 21 days.

FIG. 2. *H. capsulatum* showing tuberculate chlamydospores from room temperature culture. 864×.

aerial mycelium which turns buff to brown (plate IV, figure 1). Preparations for microscopic examination in lactophenol cotton blue reveal the characteristic, large, thick-walled, tuberculate chlamydospores (plate IV, figure 2). On brain-heart infusion blood agar at room temperature colonies develop in 7 days as moist, cerebriform reddish-brown growths which must be transferred to Sabouraud's glucose agar for characteristic spore development. If the mycelial phase is transferred to Blood agar slants which are sealed with paraffin and incubated at 37°C., the tissue or yeast phase is developed (plate IV, figure 3). This growth consists of small, oval, budding, thin-walled yeast-like cells (plate IV, figure 4).

Sputum containing *Sporotricum Schenckii* should be cultured on Sabouraud's glucose agar at room temperature and on beef infusion blood agar plus penicillin and streptomycin at 37°C. On both media colonies develop in 4 to 6 days as flat membranous growths which may be cream-colored to deep brown in color (plate IV, figure 5). Preparations for microscopic study in lactophenol cotton blue reveal delicate hyphae and conidiophores from which clusters of pyriform conidia are produced (plate IV, figure 6). Campbell (2) showed that these cultures may be reverted to the tissue or yeast phase on Francis' glucose cystine blood agar slants at 37°C. (plate IV, figures 7 and 8). Since *S. Schenckii* is rarely seen in clinical materials on direct examination, the diagnosis of sporotrichosis depends entirely on culture.

Sputum containing *B. dermatitidis* should be cultured on Sabouraud's glucose agar at room temperature and on beef infusion blood agar plus penicillin and streptomycin at 37°C. On Sabouraud's glucose agar colonies develop in 7 to 14 days as moist membranous growths which first develop tufts of aerial mycelium and finally become overgrown with white aerial mycelium which becomes buff to brown in color (plate IV, figure 9). Preparations for microscopic examination in lactophenol cotton blue reveal branching, septate hyphae with pyriform to round conidia produced directly from the sides or on short stalks (plate IV, figure 10). On beef infusion agar at 37°C., the colonies develop in 7 to 10 days as moist, heaped, cerebriform growths which are composed of budding yeast-like cells (plate III, figures 11 and 12). Heavily contaminated blood plates may be held

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FIG. 3. *H. capsulatum* on brain-heart infusion blood agar at 37°C; 5 days.

FIG. 4. *H. capsulatum* showing yeast cells from culture at 37°C. 700×.

FIG. 5. *S. Schenckii* on Sabouraud's glucose agar at room temperature; 6 days.

FIG. 6. *S. Schenckii* showing delicate hyphae and clusters of spores. 790×.

FIG. 7. *S. Schenckii* on Francis' glucose cystine blood agar at 37°C.; 5 days.

FIG. 8. *S. Schenckii* showing yeast cells from culture at 37°C. 790×.

FIG. 9. *B. dermatitidis* on Sabouraud's glucose agar at room temperature; 14 days.

FIG. 10. *B. dermatitidis* showing hyphae and spores from room temperature culture. 790×.

FIG. 11. *B. dermatitidis* on beef infusion glucose agar at 37°C.; 10 days.

FIG. 12. *B. dermatitidis* showing yeast cells from culture at 37°C. 790×.

FIG. 13. *B. dermatitidis* on streaked blood agar plate at 37°C. for one week. Filamentous colonies appeared among bacterial colonies after culture was removed to room temperature.

FIG. 14. *B. brasiliensis* on Sabouraud's glucose agar at room temperature; 21 days.

FIG. 15. *B. brasiliensis* on beef infusion glucose agar at 37°C.; 7 days.

FIG. 16. *B. brasiliensis* showing multiple budding cells from culture at 37°C. 790×.

at 37°C. for one week and then placed at room temperature until fungus colonies develop among the bacterial colonies (plate III, figure 13). Such growths should be transferred to Sabouraud's glucose agar to obtain pure cultures. The yeast-like tissue phase may be obtained by transferring the filamentous room temperature cultures to blood agar for incubation at 37°C.

Sputum containing *B. brasiliensis* should be cultured on Sabouraud's glucose agar at room temperature and on beef infusion blood agar plus penicillin and streptomycin at 37°C. On Sabouraud's glucose agar colonies develop slowly in 14 to 21 days as heaped cerebriform growths which gradually produce a short white aerial mycelium (plate IV, figure 14). Preparations for microscopic examination in lactophenol cotton blue reveal narrow and wide septate hyphae, many chlamydospores but few, if any, conidia. Identification based on room temperature cultures may prove difficult. Cultures incubated at 37°C., however, become wrinkled or granular and yeast-like (plate IV, figure 15). Microscopically, they are composed of single and *multiple* budding yeast-like cells which are characteristic (plate IV, figure 16). Since *B. brasiliensis* is found only in South America, it should be considered only if the history of the patient reveals travel in that part of the world.

PATHOGENICITY TESTS

Most of the fungi known to cause pulmonary infections are pathogenic for one or more laboratory animals. Unfortunately, however, with many of the fungi little is known about the standard doses needed to produce regularly a progressive lesion and death of the experimental animal.

Rosebury *et al.* (16) in 1944 discussed the pathogenicity of *A. bovis*. Only occasionally can progressive disease in laboratory animals be produced with this fungus. The pathogenesis of this disease is not well known and identification of the organism is based on its cultural and staining characteristics rather than on its ability to produce experimental infection.

N. asteroides produces infection and death in guinea pigs in about one week if given intraperitoneally in a sufficiently large dose. Acute peritonitis, with abscesses on the peritoneal surfaces, abdominal organs, and in the omentum, readily yields the characteristic acid-fast *N. asteroides*. Drake and Henrici (5), however, found strains to differ in their pathogenicity.

C. neoformans is pathogenic for mice although there are marked strain differences. An intraperitoneal injection of 0.5 ml. of a heavy suspension may produce death in one to three weeks. Gelatinous masses are found in the peritoneal cavity, and lesions in the liver, spleen, lungs, and brain will yield the encapsulated yeast-like cells. Intracerebral injection of mice with 0.02 ml. of a saline suspension produces cranial edema in 5 to 7 days. The fungus can be recovered from these lesions. Since some saprophytic strains of *Cryptococci* are culturally similar and have capsular material, final identification of a culture should be based on its pathogenicity for mice.

C. albicans is the only species of the genus capable of producing death of experimental animals. Benham (1) showed that 1.0 ml. of a 1 per cent suspension

of *C. albicans*, when injected intravenously, regularly killed rabbits in 4 to 5 days. The fungus can be recovered from abscesses in the kidneys.

G. candidum is imperfectly understood in regard to its pathogenicity. There have been no studies of experimental infection with this fungus.

C. immitis is pathogenic for several laboratory animals: mice, rabbits, guinea pigs, et cetera. Clinical materials or cultures will establish infection in guinea pigs inoculated intraperitoneally. Intratesticular injection of a rabbit with a suspension of arthrospores obtained from culture will yield pus containing typical endospore-filled spherules in 4 to 5 days. Although many strains may be identified morphologically, it may be necessary to identify some strains by this procedure.

H. capsulatum produces lesions and death of experimental animals irregularly when either the filamentous or yeast-phase cultures are used. Mice, rats, guinea pigs, rabbits, monkeys, and dogs have been used by various investigators. Tager and Liebow (22) reviewed the literature concerning experimental infection and described their results with mice. Although the filamentous and yeast-phase cultures have been shown to produce infection in animals, this technique is of little use with clinical materials.

S. Schenckii produces experimental infection in mice and rats when either the filamentous or yeast-phase cultures are injected intraperitoneally. The animals usually develop peritoneal and scrotal lesions from which the fungus may be recovered. Smears of pus stained by Gram's method reveal gram-positive fusiform and round budding bodies. Such tissue forms are rarely seen in clinical materials, and cultures furnish the best means of diagnosis.

B. dermatitidis produces experimental infection in mice when either the filamentous or yeast-phase cultures (one ml. of 1:200 suspension of cells) are injected intraperitoneally or intravenously. Heilman (7) found the time of death to be related to the number of organisms injected. Large caseous nodes in the mesentery and tubercles in the spleen, liver, and lungs yield the *single* budding tissue phase of the fungus.

B. brasiliensis produces lesions and death of experimental animals irregularly when either the filamentous or yeast-phase cultures are used. Intratesticular injection of guinea pigs results in a localized lesion which tends to heal spontaneously. Conant and Howell (4) showed that intraperitoneal injection of mice with 1.0 ml. of a 1:200 suspension of the yeast-phase killed mice after varying periods of time. Lesions appearing on the peritoneal surface, liver, spleen, and diaphragm yield the *multiple* budding tissue phase of the fungus.

SENSITIVITY TESTS

Many patients with fungus infections show sensitivity to the invading organism or its products and an intradermal injection of an appropriate antigen results in a tuberculin-type delayed reaction. In coccidioidomycosis, blastomycosis, and histoplasmosis the antigen usually employed, as described by Emmons *et al.* (6), is a sterile filtrate of a synthetic broth medium in which one or more strains of *C. immitis*, *B. dermatitidis*, and *H. capsulatum*, respectively, have been

grown. Some cross reactions occur with the use of these materials. In a recent paper, however, Smith *et al.* (21) have shown that these materials can be used if the proper dilutions and multiple tests are given.

The interpretation of the positive test is the same as that applied to the tuberculin test. A positive test implies *past* or *present* infection and is not used diagnostically. Also, the test becomes negative in the acutely ill patient as a result of anergy. The following materials have been used to demonstrate sensitivity to the fungi acquired during apparent or inapparent infections.

(a) *Coccidioidin* is a sterile filtrate of a synthetic broth in which one or more strains of *C. immitis* have been grown for long intervals. An intradermal injection of 0.1 ml. of a 1:100 dilution of properly standardized coccidioidin will elicit a positive skin test in 24 to 48 hours, if the patient does have or has had coccidioidomycosis. It is not a diagnostic test.

(b) *Histoplasmin* is a sterile filtrate of a synthetic broth in which one or more strains of *H. capsulatum* have been grown for long intervals. An intradermal injection of 0.1 ml. of a 1:1,000 dilution of properly standardized histoplasmin will elicit a positive skin test in 24 to 48 hours, if the patient does have or has had histoplasmosis. It is not a diagnostic test.

(c) *Blastomycin* is a sterile filtrate of a synthetic broth in which one or more strains of *B. dermatitidis* have been grown for long intervals. An intradermal injection of 0.1 ml. of a 1:1,000 dilution of properly standardized blastomycin may or may not elicit a positive skin test in 24 to 48 hours, if a patient does have or has had blastomycosis. It is not a diagnostic test.

(d) *B. vaccine* is a heat-killed suspension (1:1,000 packed cells by volume) of the yeast phase of *B. dermatitidis* grown on blood agar at 37°C. An intradermal injection of 0.1 ml. of this vaccine may or may not elicit a positive skin test in 24 to 48 hours, if the patient does have or has had blastomycosis. It is not a diagnostic test.

(e) *Monilia vaccine* is a heat-killed suspension (1:1,000 packed cells by volume) of *C. albicans*. An injection of 0.1 ml. of this vaccine gives a high percentage of positive reactions in adults. Its use is of doubtful value.

(f) *S. vaccine* is a heat-killed suspension (1:1,000 packed cells by volume) of *S. Schenckii* grown on Francis' glucose cystine blood agar at 37°C. An intradermal injection of 0.1 ml. of this vaccine will elicit a positive skin test in 24 to 48 hours, if the patient does have or has had sporotrichosis. Also, a carbohydrate obtained from *S. Schenckii* elicits a positive skin test. These tests are not diagnostic.

SEROLOGIC TESTS

In coccidioidomycosis, histoplasmosis, and blastomycosis, where the complement fixation tests have been used most extensively, a positive test is believed to be indicative of an active, progressive disseminated infection. Such a test, therefore, is a diagnostic test. Furthermore, it is an aid in prognosis as it has been shown that with progressive infection the titer rises, whereas with recovery the titer gradually falls. For years Smith (20) has used properly standardized coccidioidin as an antigen for complement fixation tests in coccidioidomycosis. Histoplasmin and/or the yeast phase of *H. capsulatum* have been used by Salvin (17), Saslaw and Campbell (18), Campbell and Saslaw (3), and Tenenberg and

Howell (23) as antigens in a complement fixation test for histoplasmosis. Also a collodion agglutination test has been used by Saslaw and Campbell (19), and a sensitized sheep cell agglutination test has been used by Norden (15) in histoplasmosis. Saslaw and Campbell (19) and Martin (12) have used blastomycin and/or the yeast phase of *B. dermatitidis* as antigens in a complement fixation test for blastomycosis.

Cross reactions are known to occur between *Blastomyces* antigens and antiserum against *H. capsulatum*; conversely, cross reactions occur between *Histoplasma* antigens and antiserum against *B. dermatitidis*. Such cross reactions, however, do not invalidate the tests as the homologous serum reacts in higher dilution. On this basis, therefore, any serum tested probably should be tested against both *Blastomyces* and *Histoplasma* antigens.

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SUSCEPTIBLE, RESISTANT, AND DEPENDENT TUBERCLE BACILLI ISOLATED FROM PATIENTS TREATED WITH STREPTOMYCIN[1, 2]

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Since the introduction of streptomycin into the therapy of tuberculosis, one of the major problems which has arisen is the accumulation of strains of bacilli which are resistant to streptomycin (1–10). This phenomenon, occurring in a large percentage of patients treated for any length of time, has been a definite limiting factor in the use of the drug. It has imposed upon the clinician the tasks of careful selection of patients for treatment and of determining the timing of therapy in relationship to other definitive procedures in the long-range plan for each patient.

The present report concerns data obtained from a small series of patients over a period of time during which laboratory work was done by uniform methods uuder the supervision of the same individuals, and the clinical management of the patients was conducted with due respect for the limitations of the drug.

MATERIALS AND METHODS

Primary isolation of tubercle bacilli from sputum, gastric contents, or other sources was made on Loewenstein's medium in the bacteriology laboratory of the University Hospital. The organisms were then inoculated into Dubos liquid medium (11) with 0.02 per cent Tween 80 and subcultured once in the same medium, so that moderate turbidity was obtained in 3 to 5 days' incubation at 37°C. This subculture was then inoculated in 0.1 ml. amounts into a series of tubes of 5.0 ml. of medium containing streptomycin in concentrations of 0.0 (control), 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 10, 20, 30, 40, 50, 80, 100, 500, and 1,000 γ per ml. The presence or absence of growth at the end of 14 days' incubation at 37°C. was accepted arbitrarily as the end-point of the test. The lowest concentration of streptomycin which inhibited growth at that time was taken as the sensitivity of the particular culture under study.

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Composition of Medium:

Basal Medium

1. Mineral concentrate

Na_2HPO_4-$7H_2O$	9.36 Gm.
KH_2PO_4	2.00 Gm.
Sodium citrate-$5\frac{1}{2}H_2O$	3.60 Gm.
$MgSO_4$-$7H_2O$	1.20 Gm.
Distilled water	100.00 ml.

The pH was adjusted to approximately 7.2.

2. Stock Medium

Mineral concentrate	100.00 ml.
N-Z Amine B (5 per cent in H_2O)	40.0 ml.
Vegex (5 per cent in H_2O)	4.0 ml.
Ferric ammonium citrate (100 mg. per ml. in H_2O)	1.0 ml.
Distilled water	800.0 ml.
Asparagine	2.0 Gm.

Before autoclaving, 10 per cent Tween 80 in water was added to make a final concentration of 0.2 ml. per 100 ml. of medium.

Before inoculating, 25 per cent dextrose in water was added to make a final concentration of 2.0 ml. per 100 ml. of medium.

Moreover, 5 per cent bovine albumin (Fraction V) in 0.85 per cent NaCl in water, pH 7.0, filtered and heated to 55°C. for 30 minutes was added to make a final concentration of 10 ml. per 100 ml. of medium.

In addition, during the latter part of the study a number of sensitivities were also determined by direct inoculation of concentrates of sputum or gastric contents on to a modification (13, 14) of Herrold's egg yolk agar (15) containing 0.0, 1.0, 10 and 100 γ of streptomycin per ml. of medium. Except where specifically mentioned, however, the sensitivities reported here are those obtained from Dubos liquid medium.

Data were obtained on 114 patients who had tuberculosis of various organs. Of these, 93 had pulmonary tuberculosis only. Among the 17 with miliary and/or meningeal tuberculosis were 7 patients with pulmonary lesions who were discharging *M. tuberculosis* in their sputum, and these 7 are included in the analyses of the sputum studies. Table 1 lists the types of disease included in this study.

Various factors, which will be discussed later, contributed toward the inclusion of cases with predominantly exudative disease and the exclusion of those with extensive pulmonary destruction who were acutely ill. This series is, therefore, probably more heavily weighted with patients having moderately advanced, predominantly exudative disease than are most of those reported. Collapse measures were used liberally in conjunction with streptomycin in the later period of the study.

The dosage of streptomycin in pulmonary cases has varied throughout the study. It is possible, however, to divide the patients into two major groups within which the variations are of minor importance. The patients in Group A received streptomycin in daily amounts exceeding 1.0 Gm., the majority receiving between 1.5 and 2.0 Gm. The Group B patients received 1.0 Gm. or less per day and, of these, all but 2 received 1.0 Gm. per day.

RESULTS

It is customarily considered that organisms which are capable of multiplying in the presence of 10 γ per ml. concentrations of streptomycin have a sufficient degree of drug resistance to be clinically significant (8, 10, 16, 17, 18). It is likely, however, that those which have become resistant to still lower concentrations may also be significant. In this report, therefore, bacilli resistant to 10 γ per ml. are considered "resistant"; those sensitive to 10 γ per ml. but growing in concentrations from 2.0 to 5.0 γ per ml. are included in some of the analyses and are termed "intermediate"; those inhibited by 2.0 γ per ml. are considered "sensitive."

Development of Resistance

Pulmonary cases: The analyses of the resistance studies on cultures from sputum or gastric contents concern 93 patients who had pulmonary disease alone and 7 patients with pulmonary disease coupled with miliary dissemination, a total of 100 pulmonary cases. Pre-therapy cultures obtained from 93 of these

TABLE 1

Distribution of Treated Cases

TYPE OF INVOLVEMENT	NUMBER OF PATIENTS
Pulmonary	93
Meningeal and/or miliary	17*
Renal	4*
Empyema	2*
Cutaneous sinus	1*

* 2 patients appear in more than one category.

patients were all sensitive to 2.0 γ per ml. with one exception. Eighty-seven were sensitive to 1.0 γ per ml., 5 to 2.0 but not to 1.0 γ per ml., and one required 10 γ per ml. for inhibition in spite of no obtainable history of previous treatment or contact with a treated patient. These findings are comparable to those of others (2, 3, 4, 8, 19, 20).

Figure 1 illustrates the rate of accumulation of resistant strains in the patients remaining positive at the stated intervals; 2 per cent at 21 days, 9 per cent at 42 days, 14 per cent at 63 days, 24 per cent at 84 days, 37 per cent at 105 days, and 36 per cent at 126 days or longer. Also illustrated are the percentages of patients harboring intermediate forms at the same intervals.

In figures 2 and 3 a division has been made between the patients who received the larger daily dose of about 2.0 Gm. (Group A) and those on the smaller 1.0 Gm. dose (Group B). In figure 2 it can be seen that a somewhat greater percentage of patients harbored resistant strains in Group B than in Group A (9), although the difference is not great enough to be statistically significant (21). Figure 3 likewise illustrates the greater percentage of patients in Group B with intermediate forms, especially midway in therapy.

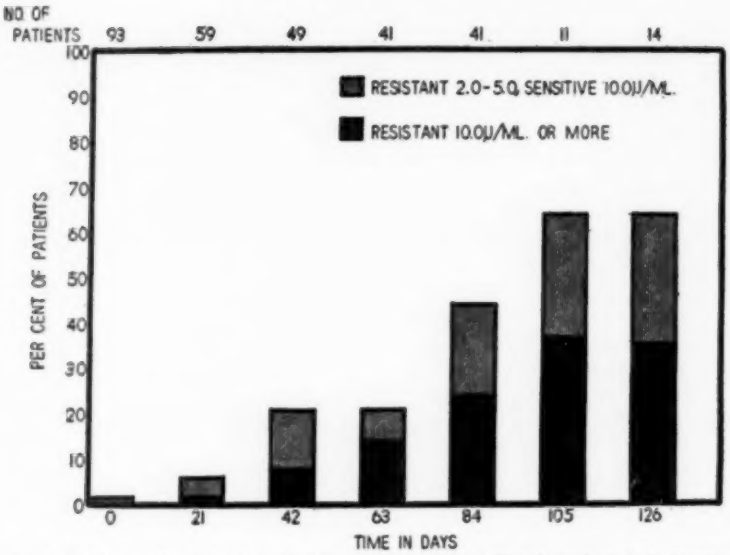
NO. OF PATIENTS 93 59 49 41 41 11 14
RESISTANT 2.0-5.0 SENSITIVE 10.0µ/ML.
RESISTANT 10.0µ/ML. OR MORE
PER CENT OF PATIENTS
TIME IN DAYS
0 21 42 63 84 105 126

FIG. 1. Incidence of resistant and intermediate strains of *M. tuberculosis* in 100 patients with pulmonary disease.

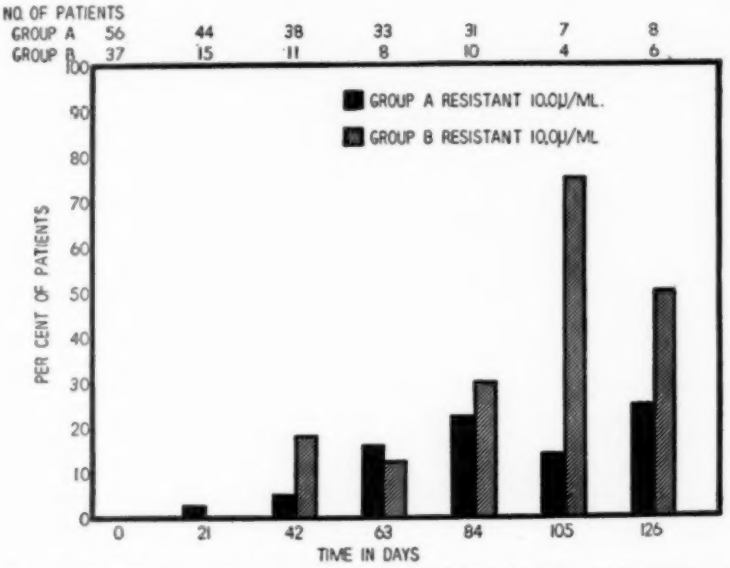
NO. OF PATIENTS
GROUP A 56 44 38 33 31 7 8
GROUP B 37 15 11 8 10 4 6
GROUP A RESISTANT 10.0µ/ML.
GROUP B RESISTANT 10.0µ/ML
PER CENT OF PATIENTS
TIME IN DAYS
0 21 42 63 84 105 126

FIG. 2. Incidence of resistant strains of *M. tuberculosis* in patients receiving streptomycin in approximately 2.0 Gm. (Group A) and 1.0 Gm. (Group B) daily doses.

Resistance at the End of Therapy

Of the 100 patients included in figures 1, 2, and 3, there were 82 who could be followed by the laboratory until the end of therapy (and beyond in all but the instances noted below). This group has been analyzed to determine the percentage of patients harboring resistant organisms after the completion of therapy. In

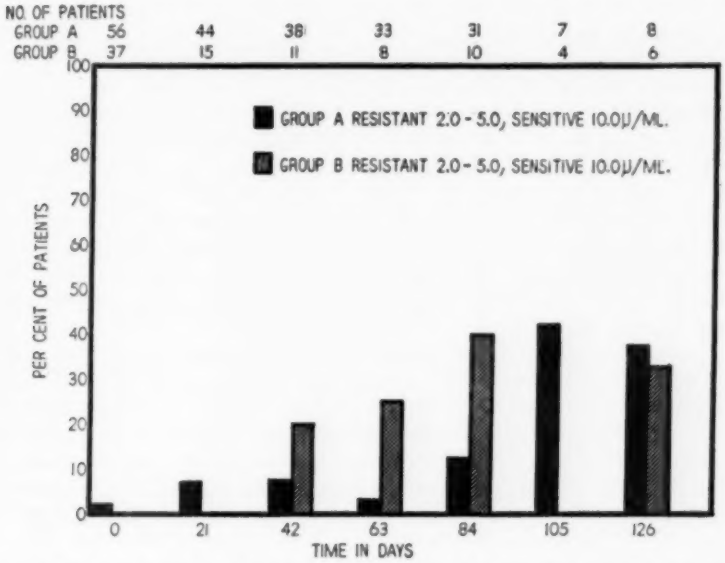

FIG. 3. Incidence of intermediate strains of *M. tuberculosis* in patients receiving streptomycin in approximately 2.0 Gm. (Group A) and 1.0 Gm. (Group B) daily doses.

TABLE 2

Sensitivity Data on 52 "Positive" Patients at End of Therapy

	GROUP A		GROUP B		
Days of therapy	78 to 100	117 to 192	40 to 54	84 to 100	120 to 134
Number of patients	22	8	3	13	6
Resistant	8 (36.4%)	2 (25.0%)	1 (33.3%)	6 (46.2%)	3 (50.0%)
Intermediate	4 (18.2%)	4 (50.0%)	0	3 (23.1%)	1 (16.7%)
Sensitive	10 (45.4%)	2 (25.0%)	2 (66.7%)	4 (30.7%)	2 (33.3%)

this analysis the occurrence of resistance is expressed in percentages of the patients who (*1*) remained positive throughout therapy; (*2*) developed resistance before converting to negative; or (*3*) reconverted to positive during the period of observation. Fifty-two patients fulfilled these conditions. Patients who "converted" and remained negative have not been included, since they are actually lost to laboratory follow-up.

Of these 82 patients, 3 reconverted after discharge and the sensitivities of their cultures are not known, and 27 converted and remained negative, giving a gross conversion rate of 33 per cent. Twenty (38.5 per cent) of the remaining 52 patients harbored resistant organisms post therapy. Table 2 analyzes these figures according to dosage and length of therapy. Ten (33 per cent) of Group A and 10 (45 per cent) of Group B harbored resistant organisms, a difference which is not statistically significant but is suggestive, particularly since the average length of therapy was shorter (by 18 days) in Group B.

Extrapulmonary cases: There are data on cultures from 15 cases of tuberculous meningitis, but cultures late in therapy are available in 4 only, since the others died early in the course of the disease or positive cultures from the cerebrospinal fluid could not be obtained. All cases of meningitis received intrathecal streptomycin, if possible, and 3.0 Gm. per day intramuscularly for 10 days followed by 1.5 Gm. per day for 110 days or longer. Thirteen of the 14 pre-therapy cultures were sensitive to 1.0 γ of streptomycin per ml; the fourteenth, isolated from the cerebrospinal fluid of the patient whose pre-therapy sputum culture required 10 γ per ml. for inhibition, also required 10 γ per ml. (This patient with miliary and meningeal disease was in the terminal stages of the disease upon admission and died the next day.)

Two cases of meningitis relapsed four and eight months after the completion of therapy and tubercle bacilli isolated from cerebrospinal fluids at the time of relapse were still sensitive to 1.0 γ per ml. Two other cases yielded organisms for study at autopsy after approximately 80 days of intramuscular and intrathecal streptomycin. In one, the organisms from the cerebrospinal fluid were resistant to 1,000 γ per ml. The second case is of particular interest in view of the difficulty encountered in attempts to demonstrate the presence of streptomycin in brain tissue from human autopsy material (22). A Negro girl was admitted with disseminated caseous tuberculosis and meningitis. Tubercle bacilli could not be isolated from her cerebrospinal fluid but those from her sputum were sensitive to 1.0 γ per ml. At autopsy on the seventy-ninth day, cultures were taken from lung, lymph nodes, and an abscess *within* the brain tissue, and all were resistant to 1,000 γ per ml.

Table 3 summarizes the findings on cultures from the remaining extrapulmonary infections.

Changes of Sensitivity post Therapy

Although it is generally agreed that bacteria tend to retain the degree of resistance attained during streptomycin therapy (2, 3, 4), it has been noted (2, 4, 5, 8) that an occasional patient with persistently positive cultures may, after therapy has been discontinued, harbor tubercle bacilli which become increasingly resistant to streptomycin, although no further contact with the drug exists. Some patients have also been seen whose organisms revert towards the sensitive state (4). The data on this subject afforded by the present series are summarized in table 4.

Dependence upon Streptomycin

The development of dependence upon streptomycin has been noted in both the pyogenic bacteria (23–27) and the mycobacteria (28–33). Tubercle bacilli dependent upon streptomycin for normal amounts of growth occurred in one patient in this series.

A white girl with far advanced pulmonary tuberculosis was reported to have received 1.0 Gm. of streptomycin daily for approximately seven months prior to her admission

TABLE 3

Post-therapy Sensitivities of Cultures from Patients with Extrapulmonary Tuberculosis

CONDITION	DAILY DOSE	THERAPY	LEAST AMOUNT INHIBITING
	grams	*days*	*γ per ml.*
Empyema	1.0	90	0.5
Empyema*	1.0	120	0.5
Renal*	1.0	120	0.5
Renal	1.0	120	0.5
Renal	1.8	150	2.0
Renal	1.0	120	100.0
Sinus	1.0	120	50.0

* Same patient.

TABLE 4

Changes of Sensitivity post Therapy

PATIENT	DAILY DOSE	THERAPY	SENSITIVITY		DAYS POST THERAPY
			End of Therapy	Post Therapy	
	grams	*days*	*γ per ml.*	*γ per ml.*	
D. S.	1.0	90	50.0	500.0	150
S. F.	2.0	90	20.0	80.0	120
V. W.	1.0	120	500.0	5.0	240
J. A.	1.8	192	20.0	10.0	70
F. T.	1.5	92	5.0	2.0	30
H. C.	1.5	120	5.0	1.0	80

to this hospital, at which time her organisms were sensitive to 3.0 γ per ml. One month after admission, streptomycin, 1.0 Gm. per day, was again administered and continued for 152 days. On the one hundred and twentieth day of therapy a sputum concentrate was inoculated directly on to several series of tubes of Herrold's medium with and without streptomycin. Numerous typical colonies appeared on all of the slants containing 1.0 or 10 γ of streptomycin per ml. of medium, while 3 of the 6 control tubes without streptomycin had no visible growth and 3 had amounts of growth estimated at 18 to 30 per cent of that in the tubes with streptomycin. A culture on the one hundred and forty-first day yielded similar results and the Loewenstein's medium inoculated from part of the same concentrate showed no growth at the end of three months. After therapy was discon-

TABLE 5

Development of Streptomycin Dependence

HOSPITAL DAYS		SMEAR OF CONCENTRATE	LOEWENSTEIN'S CULTURE	DUBOS SENSITIVITY	HERROLD'S MEDIUM			
					Per cent of Growth in			
					0	1	10	100 γ per ml.
1	Admission							
14		+	+	3.0				
35	Hemoptysis; extensive pneumonic spread by roentgenogram							
36	Hemoptysis; fever; streptomycin begun							
37	Hemoptysis							
42	Temperature subsiding							
50	Hemoptysis							
54		+	+	Contaminated				
71	Hemoptysis							
93		+	+	Contaminated				
101	Hemoptysis	+	+	5.0				
133	Promizole begun							
155		+	0					
156		+	+	80.0	15	100	50	2
168		+	0					
177		+	+	20.0	10	100	90	2
188	Streptomycin discontinued	+	0		No growth			
195		+	+		100	70	0	0
210		+	+	4.0				
230		+	+	0.5				
245		+	0		No Growth			
266	Hemoptysis							
268	Spread by roentgenogram PAS begun; streptomycin resumed	+	+	50.0	100	50	20	0
273		+	0		50	100	75	0
279		+	0		No growth			
286		+	0		50	100	80	10
292		+	0		No growth			
309		+	0		No growth			
327		+	+	50.0				
338		+	+	80.0				
359		+	0		No growth			
369		+	+	50.0				
385		+	+	50.0				

tinued, the tubercle bacilli became increasingly sensitive to streptomycin, a reversion noted as occurring with all organisms so far studied (26, 27, 31, 32). Subcultures from Herrold's medium also demonstrated a rapid loss of dependence *in vitro*. Eighty days after the end of therapy, another course of streptomycin, 1.0 Gm. per day, was begun and partial dependence of the organisms again appeared.

It is interesting that, since the middle of the first course of streptomycin in this hospital, isolation of tubercle bacilli from this patient's sputum, originally a very easy procedure, has become sporadic and unpredictable on media with or without streptomycin, although smears of the concentrates continue to show acid-fast bacilli. Table 5 summarizes the findings in this case. The growth on Herrold's medium is recorded in percentages of growth as compared with the amount of growth on the slant containing the largest number of colonies, which is taken as 100 per cent growth for that series of tubes.

DISCUSSION

There is now little doubt that the emergence of strains of bacteria resistant to streptomycin is a matter of the selection of resistant organisms (12, 30, 34). These forms, which occur genetically through mutations (35) and independently of contact with the drug, are normally present in very small numbers. In order for the resultant population to contain a high proportion of resistant bacteria, two conditions must be met: (*1*) the substrate must be satisfactory for continued bacterial growth, and (*2*) there must be a selective suppression of the sensitive organisms. To state this somewhat differently: In the presence of streptomycin, development of a high percentage of resistant forms is not likely to occur under conditions which are not otherwise conducive to continued bacterial growth.

Translating this to clinical situations requires only the assumption that, in the majority of patients, local tissue-immune reactions are bacteriostatic to a certain degree. One then arrives at an easily acceptable explanation of the variations in the development of resistance which occur in the several types of tuberculosis. For example, it is now generally accepted that a high percentage of resistance is apt to develop rapidly in the bacterial populations of patients with caseous and/or cavitary types of disease (8, 10, 20). In these patients the organisms are resident in areas which are isolated from local immune reactions of the host and in which the conditions for bacterial multiplication are usually as near optimal as obtains in the body. When streptomycin is added to such a system, the conditions are well suited to the survival and multiplication of resistant variants. On the other hand, organisms present in an area of exudative disease capable of complete, or nearly complete, resolution are in intimate contact with the host's immune factors. Thus, in predominantly exudative areas of disease the substrate, i.e., the lung, is not conducive to continued bacterial growth and addition of streptomycin would not be expected to lead to a rapid *accumulation* of resistant forms. This also fits in well with the observations that the more seriously and acutely ill patients are prone to rapid development of resistant bacteria (6, 8), since they can be assumed to have poor immunity and ultimately have considerable tissue necrosis.

Carrying this thesis a step further, clinical evidence has demonstrated the value of collapse procedures in the management of more advanced forms of tuberculosis in which cavitation and caseation are prominent. Although the mechanism of action of these procedures is not entirely clear, collapse certainly results in rendering conditions less favorable for continued growth of tubercle bacilli. It seems logical, therefore, to expect that careful selection of cases for streptomycin therapy plus proper timing and liberal use of collapse measures will result in a considerable lowering of the percentage of patients harboring resistant organisms post treatment.

The experiences reported here show a lower incidence of resistant strains post therapy and a slower rate of development of resistance than the majority of the series reported (3, 5, 6, 7, 9), i.e., 15 to 29 per cent at 42 days, 53 to 74 per cent at 56 to 63 days, 44 to 92 per cent at 84 days, and 52 to 97 per cent at 120 days or longer, although they agree fairly well with the findings in occasional reports (2, 4).

These differences are believed not to be due to technical deviation or to error, but probably to several factors which can be explained on the basis of the above discussion. In the first place, during the early phases of the study, cases with early exudative disease were deliberately selected for streptomycin therapy (36). Secondly, by the time this phase of the study was completed, sufficient clinical experience had accumulated to define some of the limitations of streptomycin in the more extensive cases where caseation and cavitation are prominent. As a consequence, in later phases surgical and medical collapse measures were used liberally in conjunction with streptomycin. And, finally, the nature of this institution is such that fewer patients acutely ill with advanced disease are admitted and retained.

Considerable discussion has taken place concerning the relative merits of the several media and methods employed in measuring the susceptibility of the tubercle bacillus to antibiotics (2, 4, 37–39). It is our impression, from incomplete data in this laboratory, that there are few consistent and significant differences among the various systems advocated. One cannot reproduce in the test tube the conditions which exist within the body and arbitrarily selected end-points do not give a complete picture of the varying proportions of organisms of different degrees of sensitivity present in the several possible foci (4, 12, 13). Thus establishment of a simple reproducible method for standard use would seem the more important aspect of the problem.

The size of the daily dose of streptomycin has been reduced frequently in attempts to avoid or minimize the toxic side effects of the drug, and there have been much speculation and experimentation on the effect of small doses on the emergence of resistant strains (5, 13, 20, 40–42). The most consistent difference in the results obtained with the two dosages used in this series, aside from a slightly higher rate of development of resistance in the patients receiving the smaller (1.0 Gm.) daily dose, has been the greater incidence during the middle stages of therapy of strains of "intermediate" resistance in this same group (figure 3). The scarcity of these forms in the cultures from patients on the larger (2.0 Gm.)

dose is probably a reflection of the higher concentrations of streptomycin maintained in the body fluids by the larger amounts administered (22, 43, 44). Such concentrations could be expected to suppress the growth of organisms of lesser degrees of resistance. The exact clinical significance of the accumulation of forms of intermediate resistance is not known, but it is logical to expect that some degree of antibacterial effect may be lost (17, 45).

It has been shown (4) that only 0.1 per cent of a population of tubercle bacilli need be resistant to a given concentration of streptomycin to produce growth in that concentration in liquid media. This being so, the tendency of occasional resistant cultures to revert to sensitivity after the cessation of therapy can be explained by their overgrowth by the more sensitive strains which are released from the suppressive action of streptomycin. The phenomenon of a continued increase in resistance after therapy is less easily explained, since it has been suggested (18) that, if there is any difference in the growth rates of the variants, that of the resistant strains is probably slower than that of the sensitive parent forms.

Since biologic methods of assay have failed to demonstrate significant amounts of streptomycin in the brain substance (22), isolation of highly resistant organisms from an abscess which was entirely enclosed in brain tissue, in the case briefly reported here, assumes further interest. It is obvious that, since the central nervous system symptoms were present before streptomycin was administered and while the more accessible bacilli from other organs were still highly sensitive, the drug must have penetrated into the brain substance itself in order to have induced an accumulation of resistant bacteria.

Demonstration of dependence upon streptomycin in an organism isolated directly from a patient is, as yet, rare (29), and the clinical implications of such a demonstration are by no means clear. It seems certain that development of resistance is a genetic trait that occurs independently of contact with the drug (12, 31, 34, 35). On the other hand, the very labile behavior of the organisms during periods of dependence followed by reversion to sensitivity (31, 32) argues a change induced by the presence of the drug. Without direct inoculation of sputum concentrates on to Herrold's or other media into which streptomycin can be incorporated, this phenomenon will not be detected ordinarily, since dependent organisms will be lost during culture on routine media. While it is assumed to be relatively rare, it may be found to be less so, especially in patients who receive treatment for prolonged periods of time, if primary isolation on solid media with and without streptomycin becomes more generally employed.

SUMMARY AND CONCLUSIONS

Data are presented concerning the development of streptomycin resistance by tubercle bacilli from 114 cases of tuberculosis treated with streptomycin. Studies of organisms isolated from meningitis in relapse and of those obtained after therapy was discontinued are included.

Disappearance of *M. tuberculosis* from the sputum occurred in 27 (33 per cent) of the 82 pulmonary cases which could be followed adequately in this laboratory. Resistance appeared at a rather slow rate; 9 per cent at 42 days, 14 per cent at

63 days, 24 per cent at 84 days, with a final rate of 38.5 per cent of all 82 patients. This is somewhat slower than the rates generally reported and the reasons for this are discussed.

A case is reported in which tubercle bacilli developed dependence upon streptomycin, in that they required streptomycin for normal growth, and reverted to sensitivity when therapy was discontinued.

SUMARIO Y CONCLUSIONES

Bacilos Tuberculosos Susceptibles, Resistentes y Dependientes Aislados de Enfermos Tratados con Estreptomicina

Los datos presentados versan sobre la formación de resistencia a la estreptomicina por los bacilos tuberculosos de 114 casos de tuberculosis tratados con estreptomicina. Agréganse estudios de microbios aislados de meningitis en recidivas y de los obtenidos después de abandonar la terapéutica.

Hubo viraje (no meramente pasajero) del esputo en 27 (35 por ciento) de los 82 casos pulmonares que pudieron ser observados adecuadamente en el laboratorio. La resistencia apareció con alguna lentitud (9 por ciento a los 42 dias, 14 por ciento a los 63 dias, 24 por ciento a los 84 días, con un coeficiente final de 38.5 por ciento de todos los 82 enfermos). Esto es algo más lento que los coeficientes comunicados generalmente, discutiéndose aquí las razones de ello.

Comunícase un caso en que los bacilos tuberculosos mostraron dependencia de la estreptomicina, por exigir estreptomicina para su crecimiento normal y recobrar la sensibilidad al suspenderse la terapéutica.

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STREPTOMYCIN-RESISTANT TUBERCLE BACILLI[1]

Incidence in Cases Treated with Different Dosage Schedules

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The development of bacterial resistance has been the major handicap in the use of streptomycin for the treatment of tuberculosis. A number of different streptomycin dosage schedules have been devised in the hope of delaying or preventing emergence of resistant strains of tubercle bacilli in patients receiving streptomycin therapy. In order to compare properly the value of different dosage schedules, it is necessary (a) to employ a statistically significant number of patients on each regimen; (b) to perform the *in vitro* sensitivity determinations by the same method, preferably in the same laboratory; (c) to use the same criterion of resistance; and (d) to compute the results in the same manner.

This report presents the incidence of resistant strains of tubercle bacilli encountered using nine different dosage schedules which have been employed in the treatment of more than 500 cases of pulmonary tuberculosis at Fitzsimons General Hospital. Only those regimens for which adequate bacteriologic data have been accumulated on 20 or more cases are included. No attempt is made here to correlate clinical response or pathology with development of resistance.

METHODS

Twenty-four-hour sputum specimens or fasting gastric washings were concentrated by the trisodium phosphate method (1) and inoculated on one tube of Petragnani's medium. Cultures were incubated at 37°C. and examined weekly, an average of four weeks being required for adequate growth to occur on this medium. If no visible growth was present after seven weeks' incubation, the culture was called negative and was discarded.

Positive cultures were subcultured with a stiff loop into Tween-albumin medium (2) in order to provide a homogenous inoculum for sensitivity determinations. Care was taken to remove representative portions or all of the growth in order to minimize the effect of resistant variants. Most of the subcultures were well grown after seven to fourteen days' incubation. They were then allowed to stand or were centrifuged gently and the supernatant fluid poured off aseptically. This procedure provided a heavier inoculum for sensitivity determination. One large loopful of this sediment was then planted on four (screw-capped) tubes of Herrold's egg yolk agar (3) containing 0, 1, 10, and 100 γ of streptomycin per ml. These tubes were incubated for ten to fourteen days at 37°C. and examined under a strong light. Growth on the control tube was arbitrarily considered four plus and growth on the other tubes was evaluated in terms of the control. One to 25 per cent of the control was considered as one plus, 26 to 50 per cent as two plus, 51 to 75 per cent as three plus, and more than 75 per cent as four plus.

EVALUATION OF RESULTS

Cases were placed into groups according to dosage and duration of treatment. The following definitions were used in classifying cases:

Converted: Patients who yielded positive cultures before and/or during treatment, but from whom positive cultures could not be obtained on or after the day of evaluation.

[1] From the Laboratory Service and the Tuberculosis Division of the Medical Service, Fitzsimons General Hospital, Denver, Colorado.

Sensitive: Patients with positive cultures on or after the day of evaluation whose sensitivity studies showed detectable numbers of organisms sensitive to 10 γ of streptomycin per ml. as shown by less growth on the 10 γ per ml. tube than on the control.

Resistant: Patients who yielded cultures whose sensitivity readings showed growth comparable to the control on media containing 10 γ of streptomycin per ml.

The day of evaluation corresponded with the last day of therapy in most of the cases. The status of patients receiving therapy after the day of evaluation is reported as it was on the day of evaluation. Patients who received no additional therapy, but from whom resistant cultures were later isolated, were classified as resistant on the day of evaluation. These instances will be noted in the individual analysis of the schedule in which they were found.

The data are presented in terms of numbers of patients in the individual analyses of each regimen and in terms of percentages in the master chart.

Regimen 1: Two Gm. of streptomycin daily for 120 days

Converted	13
Sensitive	23
Resistant	64
Total cases	100

The highest incidence of resistance is encountered in this group. The rate of conversion in this series is much lower than that of the others presented in this study. This is probably due to the difference in type of case treated rather than to any difference in therapeutic effect. This schedule is one of the earliest employed at this hospital, and patients who received this regimen were usually those with far advanced disease.

Regimen 2: One Gm. of streptomycin daily for 120 days

Converted	13
Sensitive	8
Resistant	16
Total cases	37

In spite of the reduction in dosage, the incidence of resistance is almost as great as with 2 Gm. daily for a similar period.

Regimen 3: One Gm. of streptomycin daily for 42 days

Converted	46
Sensitive	71
Resistant	16
Total cases	133

Shortening the treatment period from 120 to 42 days has reduced the percentage of resistant cases (calculated on the basis of patients with positive cultures on the day of evaluation) from 67 to 18.4 per cent. This trend is to be expected and is further confirmed by the analysis of regimen 4.

Regimen 4: One Gm. of streptomycin daily for 28 days

Converted	29
Sensitive	85
Resistant	3
Total cases	117

Reducing the length of treatment from 42 to 28 days further reduces the percentage of resistant patients. The 3 patients classified as resistant in this series were sensitive at the end of therapy, but yielded consistently resistant cultures within thirty days after treatment was stopped. Detailed clinical studies of this group will be reported elsewhere (4).

Regimen 5: 0.5 Gm. of streptomycin daily for 28 days

Converted	9
Sensitive	19
Resistant	0
Total cases	28

Lowering the daily dosage from one Gm. to 0.5 Gm. further reduces the incidence of resistant strains.

Regimen 6: One Gm. of streptomycin daily for 28 days; no streptomycin for 42 days followed by one Gm. daily for an additional 28 days

Converted	11
Sensitive	18
Resistant	6
Total cases	35

This regimen was devised primarily for those patients who did not receive adequate clinical response from the one Gm. daily for 28 days regimen. A comparison of these figures with those of regimen 4 shows that additional therapy has increased the incidence of resistant cases. Detailed clinical studies of this group will be reported with those for regimen 4.

Regimen 7: One Gm. of streptomycin every third day for 120 days

Converted	12
Sensitive	25
Resistant	13
Total cases	50

The clinical studies and theory of intermittent streptomycin (regimens 7 and 8) will be presented in a separate paper (5). Further therapy increased the percentage of resistant cases in this group. It is concluded that, compared to similar daily dosage schedules, every three-day intermittent streptomycin therapy delays, but does not prevent, the emergence of resistant strains of tubercle bacilli in patients undergoing treatment with the drug.

Regimen 8: Two Gm. of streptomycin every third day for 120 days

Converted	24
Sensitive	17
Resistant	9
Total cases	50

The higher incidence of conversion in this series as compared to regimen 7 may be due to differences in pathologic types of cases treated. Here again intermittent

TABLE 1

Percentile Analysis of Sensitivity Studies

REGIMEN		NUMBER OF CASES	DAY OF EVALUATION	DAYS OF THERAPY*	TOTAL DOSAGE	PER CENT OF TOTAL CASES			PER CENT RESISTANT CASES (E DAY)†
Number	Description					Per cent Converted	Per cent Sensitive	Per cent Resistant	
					Gm.				
1	2 g/d/120 d.	100	120	120	240	13.0	23.0	64.0	73.5
2	1 g/d/120 d.	37	120	120	120	35.1	21.6	43.2	66.7
3	1 g/d/42 d.	133	42	42	42	34.6	53.4	12.0	18.4
4	1 g/d/28 d.	117	28	28	28	24.8	72.6	2.6	3.4
5	0.5 g/d/28 d.	28	28	28	14	32.1	67.9	0.0	0.0
6	1 g/d/28 d.; no streptomycin for 42 days; 1 g/d/28 d.	35	98	56	56	31.4	51.4	17.1	25.0
7	1 g/q 3 d. 120 d.	50	120	40	40	24.0	50.0	26.0	34.2
8	2 g/ q 3 d/ 120 d.	50	120	40	80	48.0	34.0	18.0	32.0
9	2 g/DHSM‡ q 3 d/120 d.	20	30	10	20	15.0	85.0	0.0	0.0

* Days of actual therapy.

† Computed in terms of cases with positive cultures on or after the day of evaluation.

‡ Dihydrostreptomycin.

streptomycin delays, but does not prevent, the emergence of resistant strains of tubercle bacilli.

Regimen 9: Two Gm. of *dihydrostreptomycin* every third day for 30 days

Converted	3
Sensitive	17
Resistant	0
Total cases	20

These cases did not develop *in vitro* resistance to either streptomycin or dihydrostreptomycin. The lack of development of resistance in this series is to be expected in view of the reduced dosage and short treatment period.

DISCUSSION

The incidence of resistance may be computed in two ways from the data given in the individual analyses. The first method is to calculate the percentage resistant in terms of only those patients with positive cultures on or after the day of evaluation. If this method is used, the sensitivity status of each patient is known at the time of evaluation and no unknown (converted) cases are included in the calculation.

The second method is to calculate the percentage of resistant cases in terms of the total number of patients in the series. This method is based on the observation that cultures obtained at a later date from patients who convert during therapy are usually sensitive to streptomycin (6). This observation has been confirmed in the detailed study of regimens 7 and 8 (5). Here 14 patients with a reliable index of conversion (two negative cultures a week for three months) were sensitive when positive cultures were later obtained. There were no exceptions in this series. Assuming that the converted cases should be classified as sensitive results in a lower percentage of resistant cases. Results as determined by both methods of computation are shown in table 1.

SUMMARY

An analysis of streptomycin sensitivity studies on cultures obtained from more than 500 patients is presented. A comparison is made of the incidence of *in vitro* resistance of tubercle bacilli isolated from patients on nine different streptomycin treatment regimens.

Lowering the length of the treatment period and/or the daily dosage lowers the incidence of resistant cases in patients treated with daily dosage schedules.

As compared to similar daily dosage schedules, q. 3 day intermittent streptomycin therapy delays the emergence of resistant strains of tubercle bacilli.

SUMARIO

Bacilos Tuberculosos Estreptomicinorresistentes. Incidencia en los Casos Tratados con Distintos Esquemas Posólogicos

Este análisis está basado en los estudios de la sensibilidad a la estreptomicina en cultivos obtenidos de más de 500 tuberculosos. Compárase la incidencia de la resistencia *in vitro* de los bacilos tuberculosos aislados de enfermos sometidos a nueve distintos régimenes terapéuticos de estreptomicina.

La disminución de la duración del período de tratamiento y/o de la dosis diaria hace disminuir la incidencia de casos resistentes en enfermos tratados con esquemas de dosis diarias.

Comparada con esquemas semejantes de dosis diaria, la estreptomicinoterapia intermitente a plazos de tres días retarda la aparición de cepas resistentes de bacilos tuberculosos.

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DUPLICATION OF ROENTGENOGRAMS BY ARTIFICIAL SOLARIZATION[1,2]

With Emphasis on a Simple Standardized Technique

WILLIAM H. ROPER[3]

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INTRODUCTION

In conducting a long-range survey on a group of soldiers who developed minimal tuberculosis during military service, it appeared obvious that selected chest roentgenograms of representative cases would constitute a vital element of the permanent files. The original diagnostic and "progress" films were borrowed from numerous sources throughout the country and had to be returned promptly. In response to this need, a simple technique for duplicating films was established in early 1944 and has been improved progressively.

Some workers have employed the dual step method of transferring photographically from an original roentgenogram to an intermediary positive, then back to a final negative. Such transfers involve light exposures of extremely low order, e. g., lighting and immediately extinguishing a match. The method described here, usually referred to as "solarization," requires enormously larger light exposures. The result is a reversal, giving a negative from a negative, a positive from a positive. It is interesting to note that a further marked increase of light exposure results in a second reversal, producing a positive from a negative or a negative from a positive.

Duplication of roentgenograms by means of solarization has been accomplished independently by many workers but relatively few published articles on this subject are to be found in the literature (1 through 6). Duplicates have been prepared by exposure to roentgen rays or to light rays, either solar or artificial. Most workers have used commercial double-emulsion X-ray film. Some have advocated preliminary fogging of the fresh film by a relatively brief light exposure.

This report describes a simple standard technique for single-phase direct duplication of a negative from an original roentgenogram without preliminary fogging.

EQUIPMENT

1. The source of light is a 500-watt reflector-type fotoflood bulb, GE #RFL-2, in a fixed and rigid overhead socket. In order to minimize divergence of the rays of light, the distance

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[1] From the Section for Research on Minimal Tuberculosis, Army Medical Research & Development Board, and University of Colorado Medical Center, at Fitzsimons General Hospital, Denver, Colorado.

[2] This study was part of a project initiated in January 1944 with Dr. James J. Waring as Responsible Investigator and with Col. (retired) George F. Aycock and ex-Col. Esmond R. Long as Consultants. The author was Director of the Section.

[3] Birmingham Veterans Administration Hospital, Van Nuys, California.

between the bulb and the target should exceed 36 inches. As the distance increases, the exact intensity of delivered light decreases and thus the exposure time must be increased. A distance of approximately 50 inches has given good results. One source of streaking on the duplicates may be the etched trademark on the "face" of the bulb. Surprisingly, this may be eliminated by putting a spot of ink over a small central portion of the etching. The life expectancy of this particular bulb is approximately six hours.

2. A large vacuum-type contact printer, capable of handling 14 by 17 films is desirable but not essential. In lieu of this equipment, excellent results can be procured by employing a pressure-type printing frame with clamps (7); or even by laying a flawless 14 by 17 ground-edged sheet of heavy plate glass on top of the films just prior to exposure, aligning by touch the edges of the unexposed film, the original film, and the superimposed glass. Regardless of the type of printing equipment employed, an immediate base of black cardboard or heavy paper is advisable to furnish a smooth surface for the films and to minimize the potential factor of back reflection of light. For convenience in aligning the edges of the films, this base should measure the same size as the films to be handled.

3. Eastman Blue Brand double-emulsion film, as used ordinarily for roentgenograms, gives optimal results. Dupont film of similar type has been tested and found to require approximately six times the light exposure for comparable results. Commerical double-emulsion Ansco X-ray film has been used also, but even larger exposures are necessary for solarization. To reduce tendency of the film towards buckling or bending, boxes of unexposed film should be stored in a cool atmosphere of moderate humidity. The unexposed films for a given session are removed carefully from the original cardboard box, each inside its protective paper, and lifted cautiously to a light-proof transfer box. Thus the film that is to remain in storage is not disturbed.

4. Any brand of developing and fixing solutions may be used. Kodalk #1 Developer and Eastman X-ray Fixer, each at 68°F., have proved very satisfactory.

5. Ordinary dark-room equipment such as timer clock, light-proof boxes for transporting of films, et cetera, are satisfactory for the described technique.

PROCEDURE

Preparation: The selected original film is cleansed gently but carefully by means of absorbent cotton swabs soaked in a solution of 3 parts of 95 per cent ethyl alcohol and 1 part of carbon tetrachloride. Dry cotton swabs are used promptly thereafter. Each type of swab is applied gently, in large-circle motion. With proper application and prompt drying, this preparation does not alter or mar the emulsion of the original film.

Identifications and legends, if desired, may be marked on a "blank" portion of the original film for photographic transfer to the duplicate. Eastman's Opaque, dark red, has been found superior to soft crayon, ink pencil, et cetera, for this purpose. Applied gently with a smooth ball-point pen, the Opaque produces neat, even, and nonsmearing lines without scratching the emulsion of the film. It can be removed readily by gentle swabbing with water-soaked cotton, followed rapidly by the drying solution of alcohol and carbon tetrachloride described above.

The character and quality of the film to be reproduced are studied on a viewbox or illuminator in an effort to anticipate the proper technique for that particular roentgenogram. Contrary to first impression, films of greater contrast or "darker" originals are reproduced better by longer exposure times, up to 360 seconds for the equipment described previously. Conversely, a "lighter and softer" original film calls for less light exposure, down to 5 or 10 seconds. The usual optimal range for original films of good quality is 20 to 60 seconds, with an average of 30 to 45

seconds. In other words, shortening of the exposure time produces a darker duplicate, whereas increase of this factor yields a "lighter and softer" one. It must be remembered that a flash exposure produces the ordinary positive print used in photography. With the equipment described above, a second positive phase will appear when the time of light exposure has exceeded 6 minutes. Correct exposure time for the negative duplicate desired will lie between these two extremes. Individual experience by each technician is essential in this important detail of anticipating the proper light-time exposures for original roentgenograms of varying techniques. Moreover, the factor of subsequent degree of developing must be kept in mind, as discussed below.

Printing: Meticulous care must be observed in all manipulations of the transfer film, both before and after its exposure to light. Solarization seems to increase considerably the sensitivity of double-emulsion film to static, emulsion reaction from buckling or bending, and other physical factors known to result in artifacts. Films should never be allowed to slide across or rub against each other. Careful lifting by means of firm finger-grips on opposite corners will reduce both buckling and static-producing friction.

The unexposed film is laid carefully on the black cardboard or paper, in the vacuum printer or clamp frame, or on the table. The original film then is laid carefully on top of the unexposed one to which the image is to be transferred. All edges of the two films are aligned as accurately as possible with each other and with the underlying black-base surface; however, avoidance of sliding friction is of far greater importance than perfect alignment of film edges. The printing frame is closed, or the plate glass is laid carefully on top of the films. Perfect contact of the original and the unexposed film, with even distribution of pressure, is of utmost importance.

The overhead floodlight is then switched on for the period of time which has been judged as optimal for the original roentgenogram being duplicated.

Reversing the placement procedure, the printer is opened or the plate glass lifted, the original film is lifted gently and laid aside, and the solarized film is transferred carefully to a light-proof transporting or loading box. Even if the developing equipment is located in the same immediate unit as the printing apparatus, it is wise to complete the printing of several to approximately twelve films at a time before proceeding to the developing phase.

Developing: Experience has demonstrated that a better over-all duplicate is produced under conditions of partial underdevelopment than with full or complete processing. The aforementioned light exposure times are based on this technique of incomplete development. For the printing technique described above, processing of 50 to 60 seconds (more rarely up to 75 seconds) in Kodalk #1 Developer at 68°F. appears to yield optimal results. The films are then "fixed" fully in any ordinary "hypo" solution.

The number of films to be processed at one time must be adjusted according to the size of the tanks being used. In general, only two should be developed at a time. Until after the "fixing" phase has been reached, great caution must be observed regarding contact with other films or hangers, or with the sides of the tank.

In order to test graphically the transfer of varying film densities, a stepladder roentgenogram furnished by Dr. George C. Henny was reproduced by the tech-

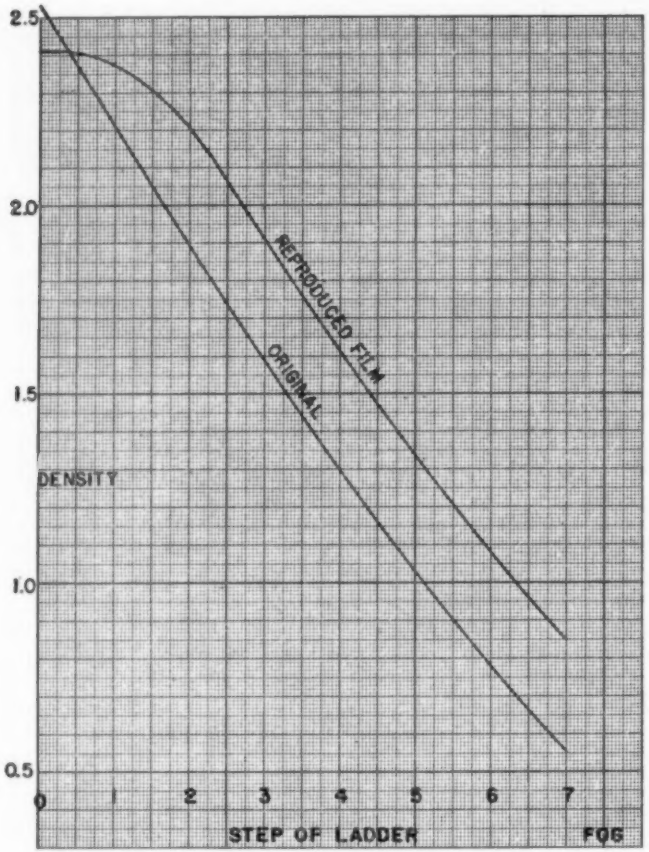

FIG. 1. The original roentgenogram was of an aluminum step wedge, having seven steps. The densities of zero step (no overlying aluminum) and of the successive steps were measured, first on the original roentgenogram and then on the reproduced film. The curves were plotted from these measurements. The reproduced film is seen to be somewhat darker than the original (indicating slightly less-than-ideal light exposure). The contrast (as indicated by the slopes of the curves) is essentially identical for the diagnostic part of the density range.

nique described. Readings of the original and the transfer films were made by means of a densitometer and recorded on the accompanying graph, figure 1, which was also obtained through the courtesy of Dr. Henny. The densitometer

readings of the two films are seen to be parallel throughout the ordinary visual ranges of 0.9 through 2.3, although they start to diverge sharply at either extreme of the scale.

Examples of the transfer films in this series have been reviewed, in direct comparison with the original roentgenograms from which they were prepared, by groups of leading roentgenologists and chest specialists throughout the country. The consensus has been that (*1*) the reproductions are of excellent general quality, (*2*) the transfer of lesion shadows is valid, and (*3*) often a superior reproduction can be prepared from an original film which is of inferior quality, due either to faulty technique or to age.

SUMMARY

A simple and standardized technique is presented for duplication of roentgenograms by artificial solarization. Some of the pitfalls and hazards of this or similar procedures are discussed.

SUMARIO

Duplicación de los Roentgenogramas por la Solarización Artificial, Haciendo Hincapié en una Sencilla Técnica Normalizada

Al presentar una sencilla técnica normalizada para duplicar radiografías por la solarización artificial, puntualízanse algunos de los riesgos y contingencias que rodean a éste y otros procedimientos semejantes.

Acknowledgments

The author is indebted to Drs. W. Edward Chamberlain, Professor of Radiology, and George C. Henny, Professor of Medical Physics, of Temple University for their technical and professional advice; also to the numerous other roentgenologists and chest specialists who cooperated in comparing the reproductions with the original roentgenograms.

Considerable appreciation is expressed to the following X-ray technicians of the United States Army who assisted with the development of this technique, in chronological sequence as named: Ex-Sgt. Morton G. Reifer, ex-T/3 John R. Zitnik, and M/Sgt. Alfred G. Smith. Each of these men contributed interest, effort, and time well in excess of "normal line of duty."

Finally, all concerned are grateful to Brigadier Generals Omar H. Quade and Edwin H. Roberts, respectively former and current Commanding Generals of Fitzsimons General Hospital, and to Colonel William S. Stone, Chairman of the Army Medical Research and Development Board, for their guidance and for their assistance in furnishing the personnel and equipment essential to this study.

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BACTERIOSTATIC AND BACTERICIDAL EFFECTS OF PRODUCTS OF SARCOID LYMPH NODES ON THE TUBERCLE BACILLUS[1,2]

SOL ROY ROSENTHAL

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INTRODUCTION

It has long been suspected that sarcoidosis may be a form of tuberculosis (1). If the tubercle bacillus is the underlying etiologic agent of this disease, the microorganisms must be destroyed shortly after they enter the host, for they are rarely recovered from pure sarcoid lesions. Kryle (2), for example, has seen tubercle bacilli in sarcoid lesions of the skin only in the early stages (ten to eleven days), but failed to note organisms in the later manifestations of the disease.

To enlarge upon this thesis, an attempt was made to determine whether or not elements present in sarcoid lesions would in some way affect the viability of tubercle bacilli. To this end sarcoid lesions were obtained from autopsy (3) and surgical specimens from source cases with negative tuberculin reactions. The lesions were emulsified and placed in contact with tubercle bacilli. Cultures on ordinary laboratory media of such emulsions yielded a group of banal organisms which were similarly tested with tubercle bacilli. The results were unequivocal in demonstrating that the emulsions and the group of organisms isolated were both bacteriostatic and bactericidal for tubercle bacilli, whereas Seitz filtrates of the sarcoid emulsions were not. Because of these observations, a similar study of the effect of sarcoid lymph nodes on tubercle bacilli has been conducted.

METHODS

The lymph nodes were all obtained from patients in whom the diagnosis of sarcoidosis had been established by examination of biopsy specimens and the absence of skin reaction to the second-strength PPD. The tissues were first minced and then emulsified in a mortar under sterile conditions. A heavy suspension was made and treated as follows:

1. The suspension was cultured directly and after digestion (in sodium hydroxide and neutralized with HCL) on egg media (Petragnani).
2. The suspension was cultured directly on brain infusion broth, blood agar plates, thioglycollate, and eosin methylene blue.
3. One ml. of the suspension was inoculated intraperitoneally into guinea pigs.
4. One ml. of emulsion was poured over a recently isolated culture of human tubercle bacilli which was approximately three weeks old.
5. One ml. of emulsion was mixed with a small loopful of human tubercle bacilli as above and was incubated for one hour at 37°C., with subsequent culture on egg media.
6. The emulsion was filtered through a Seitz filter and the filtrate was tested with tubercle bacilli as in Nos. 4 and 5.
7. Twenty- to twenty-four-hour broth cultures of the lymph node emulsion were treated as in Nos. 4, 5, and 6.

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[1] From the Institution for Tuberculosis Research, University of Illinois College of Medicine, Research Foundation, and Bruns General Hospital.

[2] This study was aided in part by a grant from the Public Health Service (Research Grant RG-788).

TABLE 1

Effect of Products of Sarcoid Lymph Nodes on Tubercle Bacilli

	GROWTH ON EGG MEDIA	GROWTH ON OTHER MEDIA	SUBCULTURE ON EGG MEDIA	SUBCULTURE ON OTHER MEDIA	REMARKS
1. Lymph node emulsion	Negative	*Micrococcus* *Staphylococcus* *Streptococcus*	Negative	*Streptococcus*	Animal inoculations in series (2); negative for tuberculosis
2. Lymph node emulsion plus tubercle bacilli	Negative	—	Negative	*Micrococcus* *Staphylococcus* *Streptococcus*	Smear from original egg media; tubercle bacilli plus other bacteria
3. Lymph node emulsion laid over culture of tubercle bacillus	Growth arrested	—	Negative	Negative	Green to yellow discoloration of colonies; no lysis
4. Broth culture. Lymph node treated as in 2 and 3	Negative	—	Negative	—	Smear from original egg media; tubercle bacilli plus *staphylococcus*
5. Filtrate of broth culture. Treated as in 2 and 3	Tbc.*	—	Tbc.*	—	Seitz filters used
6. *Micrococcus* treated as in 2 and 3	Negative	—	Negative	*Micrococcus* at 2½ weeks	Smear from original egg media tubercle bacilli and *Micrococcus*
7. Filtrate of *Micrococcus* treated as in 2 and 3	Tbc.*	—	Tbc.*	—	
8. Hem. *Staph. aureus* Hem. *Staph. albus* Nonhem. *Staph. aureus* treated as in 2 and 3	Negative	—	Negative	—	Smear from original egg media; tubercle bacilli only
9. Filtrates of 8 treated as in 2 and 3	Tbc.*	—	Tbc.*	—	
10. Alpha Hem. *Streptococcus* treated as in 2 and 3	Tbc. negative and **	—	Negative	—	
11. Filtrate of 10 treated as in 2 and 3	Tbc.*	—	Tbc.*	—	
12. Saline- and broth-treated as in 2 and 3	Tbc.*	—	Tbc.*	—	

Hem. = Hemolytic.
Staph. = *Staphylococcus.*
Tbc. = Tubercle bacilli.
* = Maximum growth.
— = Not done.
** Slight growth.

8. All microorganisms which were isolated from the lymph node were obtained in pure culture and subjected to the procedures described in Nos. 4, 5, and 6.

9. In addition to the controls as shown in No. 6, either saline or broth was used in each experiment.

Lymph nodes from three cases were studied; one was obtained from autopsy material and the other two from surgical specimens. The original incubation on egg media was three to six weeks, at which time subcultures were made on egg media, and, in many instances, on ordinary media as well. Smears were made at the time of each transfer.

RESULTS

Table 1 lists the results of one such experiment. From this table it will be noted that the emulsion of the lymph node mixed with human tubercle bacilli failed to grow on egg media, whereas a filtrate of this emulsion, or broth, or saline added to the same microorganism produced maximum growth. Subcultures on to egg media of the lymph node emulsion plus tubercle bacilli failed to grow, whereas growth in the controls continued at the maximum rate. Inhibition of young, growing cultures of human tubercle bacilli was also effected by the lymph node emulsion, and this was verified by the failure of subcultures to grow on egg media. From this particular lymph node a *Micrococcus*, three different strains of *Staphylococci*, and one strain of an alpha hemolytic *Streptococcus* were isolated. A 24-hour broth culture of these microorganisms similarly inhibited the growth of tubercle bacilli. Filtrates of the broth cultures of these organisms failed to have the inhibitory property. The alpha hemolytic *Streptococcus* seemed to have a slightly less inhibitory effect than the other bacteria. As will be shown below, the viability of the banal organisms varied. Smears at times showed tubercle bacilli alone or with the banal organisms.

In the other two lymph nodes the following organisms were isolated: Case 2: *B. coli*, *E. aerogenes*, hemolytic *Staphylococcus aureus* (autopsy case); Case 3: a *Streptococcus*, a *Staphylococcus*, and an unidentified gram-negative rod. The emulsions of these lymph nodes and the individually isolated organisms inhibited completely the growth of tubercle bacilli when they were mixed with, or poured over, young cultures of human virulent tubercle bacilli. That the action was bactericidal was indicated in every case by failure of growth upon subculturing on to egg media.

DISCUSSION

The isolation of banal organisms from lymph nodes is a common occurrence (4). The fact that a wide variety were isolated from the sarcoid lymph node studies indicates that these organisms are not specific. However, their presence in the lymph node may well influence the growth of tubercle bacilli. It can be postulated that the presence of banal organisms in lymph nodes harboring tubercle bacilli may alter their growth and physical chemical state, resulting in their calling forth a sarcoid-type lesion.

The question arises as to the manner in which the banal organisms act, i.e., endo- or eno-toxins, et cetera. Exotoxins were excluded by the fact that filtrates

of the organisms or emulsions of the lymph nodes failed to have any inhibitory effect on the growth of the tubercle bacilli. An assay of the presence of endotoxins was made by freezing and thawing the organisms until no viability was manifest or by heating at 55°C. for three hours. No inhibitory effect on tubercle bacilli was noted after such processing of suspensions of hemolytic *Staphylococcus aureus*, *Micrococcus*, *S. aureus*, and hemolytic *S. albus*. Unless some intracellular factor was destroyed by the above treatment, it can be stated that no endotoxic action was demonstrated.

To determine whether any antibiotic action of these organisms against tubercle bacilli would be the product of mutual growth on Petragnani egg media, the banal organisms were seeded on malachite green egg media and viability was determined. The results were as follows:

Hemolytic *S. aureus:* Colonies vivid blue; viable at four weeks.

Micrococcus: Pin-point green colonies same as color of media; viable at three weeks.

S. aureus: Colonies deeper blue green than media; viable at one week and not at two weeks.

Hemolytic *S. albus:* Colonies blue, blue-white, and blue-green; viable at two weeks.

When the lymph node emulsion was mixed with tubercle bacilli and grown on egg media and then subcultured on ordinary media, a *Micrococcus*, a *Streptococcus*, and a *Staphylococcus* were recovered at three to six weeks. In smears taken after five to six weeks of growth on egg media, on which tubercle bacilli plus suspensions of isolated organisms were inoculated, tubercle bacilli were seen in all, but no other organisms were noted except for the *Micrococcus*. It would seem then that the banal organisms do reproduce, but in their anabolism take up small amounts of the dye with their nutrients until a point is reached where it becomes toxic to them. Finally, the organisms will fail to stain by ordinary methods.

To determine whether or not inhibition could be effected by smaller amounts of the suspensions of banal organisms, 4 of the above were grown in broth for twenty-four hours, and 0.2 ml. and 0.5 ml. were poured over a two-week-old culture of recently isolated human tubercle bacilli. For controls broth alone was used. After two and one-half weeks, only 2 of 12 tuberculosis cultures showed a small colony that was characteristic of the tubercle bacillus, whereas the controls showed luxuriant growth of tubercle bacilli. The banal organisms were recovered from most of the culture bottles except one; in the latter no typical colonies of tubercle bacilli were noted.

The results indicate the possibility that competitive growth of the banal organisms inhibits the growth of tubercle bacilli. Such a phenomenon has been described before, beginning with Koch himself (See literature by Noster (5)). The factor of pH as an influence on the growth of tubercle bacilli is partially excluded by the fact that the media in only a fraction of these studies changed in color. By actual experimentation it was found that the media at a pH of 6.8 is light green; when more acid it becomes darker green, and when the pH reaches 0.5, it becomes yellow.

SUMMARY

Emulsions of lymph nodes from proved cases of sarcoid have bacteriostatic and bactericidal effects on virulent human tubercle bacilli. A wide variety of banal organisms have been isolated from these lymph nodes which likewise have an inhibitory effect on tubercle bacilli. Filtrates of the lymph node emulsion and bacterial suspensions fail to inhibit the growth of tubercle bacilli.

SUMARIO

Efectos Bacteriostáticos y Bactericidas de los Productos de los Ganglios Linfáticos Sarcoideos sobre el Bacilo Tuberculoso

Las emulsiones de los ganglios linfáticos de casos comprobados de sarcoides ejercen efecto bacteriostático y bactericida sobre los bacilos tuberculosos humanos virulentos. De esos ganglios linfáticos que ejercen igualmente efecto inhibidor sobre los bacilos tuberculosos, se aislaron muchos variados microbios banales. Los filtrados de la emulsión linfoganglionar y las suspensiones bacterianas no inhibieron la proliferación de los bacilos tuberculosos.

Addendum

Four additional patients with sarcoidosis who had negative tuberculin reactions had lymph nodes removed by sterile surgical technique expressly for this experiment. The lymph nodes were placed immediately in broth before opening. The cultures of this broth were negative, whereas emulsions of the lymph nodes proper gave growth of gram-positive *Diplococci* or gram-negative rods, or both. The entire experiment as cited in the above paper was repeated using lymph node emulsions, filtrates of the emulsions, and isolated organisms in the manner described above, with similar results.

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THE EFFECT OF ANTIHISTAMINIC DRUGS UPON THE TUBERCULIN REACTION[1]

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INTRODUCTION

The effect of antihistaminic drugs upon the tuberculin reaction has been studied for several years. In guinea pigs, no change in reaction was observed following a single dose of certain antihistaminic compounds prior to an intradermal injection of a strong solution of O.T. (1:10) (1). When weak solutions of O.T. (1:100 to 1:10,000) or Purified Protein Derivative (PPD) (0.005 to 0.00002 mg.) were used, however, and 50 mg. of Benadryl[2] per Kg. of body weight were administered daily in two divided doses, the intensity of the reaction and the incidence of necrosis were significantly reduced. In fact, when threshold amounts of O.T. (1:10,000) or PPD (0.00002 mg.) were given, many animals failed to develop any reaction in twenty-four hours and those which did were mostly found to be negative after forty-eight hours (2).

In man, Breton (3) reported a decrease in reaction intensity following the administration of Antergen. Similarly Judd and Henderson (4) observed that the Mantoux test became negative in 18 out of 30 tuberculous patients during prolonged treatment with large doses of antihistaminic drugs, and it was positive again four to six weeks after discontinuation of the treatment.

OBSERVATIONS

As these observations are of considerable clinical interest, we have restudied the effect of antihistaminic drugs upon the tuberculin reaction in patients chosen at random from the Division of Chronic Diseases of the Chest. Seventeen of the patients suffered from predominantly exudative tuberculosis, 66 from productive tuberculosis, while 4 had other diseases. The tuberculin reaction was positive in all patients forty-eight hours after 0.1 cc. of PPD No. 1 intracutaneously. A week after a control test, the patients were placed on a regimen of 50 mg. of Benadryl every four hours. On the second day of this treatment, they received an injection of 0.1 cc. of PPD No. 1 intracutaneously and readings were taken forty-eight hours after the injection. All readings were based on the size of the area of induration.

It was found that in most patients Benadryl effected a decrease in the size of the tuberculin reaction. The area of induration was diminished more than 25 sq. mm. in 63 patients, it was enlarged more than 25 sq. mm. in 5 patients, while the remaining 19 patients showed no appreciable change. There was no differ-

[1] From the Philadelphia General Hospital, Philadelphia, Pennsylvania.

[2] Benadryl and Neo-antergen were the antihistaminics used and these were supplied through the courtesy of Parke, Davis & Co., and Merck & Co., Inc., pharmaceutical concerns.

ence in the effect of Benadryl in patients with exudative or productive tuberculosis or in patients who had no tuberculosis at all (table 1).

In order to ascertain that the change in the reaction intensity in our patients was not caused by the sequence of measures adopted, we subjected 10 additional patients to a reversed procedure, giving Neo-antergen[2] during the first test period instead of the second. It was found that in 8 of these patients the size of the indurated area following the first injection of PPD was more than 25 sq. mm. smaller than that after the second injection.

COMMENT

The above results confirm the observations of Breton (3) and Judd and Henderson (4) in man, as well as those of Sarber (2) in guinea pigs. The absence

TABLE 1

The Effect of Antihistaminic Drugs upon the Tuberculin Reaction

TUBERCULIN REACTION	EXUDATIVE TUBERCULOSIS	PRODUCTIVE TUBERCULOSIS	NO TUBERCULOSIS
	per cent	*per cent*	*per cent**
Diminished	67	73	75
Not changed	27	23	0
Increased	6	4	25

* 4 cases only.

TABLE 2

Blood Histamine Levels in Exudative and Productive Tuberculosis

	NUMBER OF PATIENTS	AVERAGE	RANGE
		γ per 100 cc.	*γ per 100 cc.*
Normal controls	10	4	2 to 8
Exudative tuberculosis	4	10	6 to 12
Productive tuberculosis	4	5	3 to 5

of complete suppression of the tuberculin reaction in any of our patients may well be explained by their moderate exposure to antihistaminic drugs.

Concerning the mechanism of the effect of antihistaminic drugs upon the tuberculin reaction, it is interesting to note that their depressing action was the same in patients with exudative and productive tuberculosis. The pulmonary process, on the other hand, has been found to be depressed by antihistaminic drugs only in exudative, but not in productive, disease (4). The latter goes well with our own finding that patients with exudative tuberculosis, in contrast to productive cases, often have an elevated blood histamine level (table 2). These observations seem to show that the depressing action of antihistaminic drugs upon the tuberculin reaction is a local phenomenon. It appears that the drugs act either by neutralizing histamine liberated during the inflammatory reaction within the injected tissue, or by an unspecific mechanism and a constricting effect of the blood vessels (5), or both. In view of this, it might be advisable to refrain

from administering antihistaminics when skin-testing with tuberculin or any other material.

SUMMARY

Of 95 patients tested with 0.1 cc. of PPD No. 1, 73 per cent showed a depression of the tuberculin reaction following the administration of the usual therapeutic doses of Benadryl or Neo-antergen. There was no difference in this effect in patients with exudative or productive tuberculosis although patients with exudative tuberculosis often have an elevated blood histamine level, whereas productive cases have not.

The skin reactivity to tuberculin should not be attempted when antihistaminic drugs are being administered.

SUMARIO

El Efecto de los Antihistamínicos sobre la Reacción a la Tuberculina

De 95 enfermos comprobados con 0.1 cc. de PPD (Derivado Proteínico de Tuberculina) No. 1, 73 por ciento mostraron atenuación de la reacción a la tuberculina consecutivamente a la administración de las habituales dosis terapéuticas de Benardil o Neoantergén. No hubo diferencia alguna en el efecto observado en enfermos con tuberculosis exudativa o productiva, aunque los exudativos muestran a menudo un nivel elevado de histamina sanguínea, lo cual no sucedeen los otros.

No debe ensayarse la cutirreacción cuando se administran antihistamínicos.

Acknowledgment

The authors wish to express their profound gratitude to Dr. William Ehrich, Professor of Pathology at the Graduate School of Medicine of the University of Pennsylvania and Chief of the Department of Pathology of the Philadelphia General Hospital, for his guidance in the preparation of this work.

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KOJIC ACID AS AN INHIBITOR OF TUBERCLE BACILLI[1, 2]

HENRY F. LEE, BEN BOLTJES, AND WILLIAM EISENMAN

(Received for publication September 23, 1949)

INTRODUCTION

A contaminant mold appearing with cultures of tubercle bacilli on solid media was noted to produce marked inhibition of bacterial growth.[3] Filtrates produced by growing the mold on Czapek-Dox media contained a substance capable of inhibiting the *in vitro* growth of several strains of tubercle bacilli. Experiments directed toward increasing the yield of the unknown inhibitory substance in the crude filtrates resulted in adoption of a 14-day growth period for the mold in Czapek-Dox medium containing added Bacto Yeast Extract.[4] Crude filtrates produced in this manner possessed approximately one-third the activity of similarly produced filtrates from *Streptomyces griseus* (streptomycin).

OBSERVATIONS

Experiments were undertaken to demonstrate the identity or lack of identity of the unknown material in the filtrates with any known antibiotic substance. The mold was identified as *Aspergillus tamarii* by Dr. Kenneth B. Raper of the Northern Regional Research Laboratories, Peoria, Illinois.

By means of extraction procedures, color reaction with ferric chloride and finally spectrophotometric analysis, the active material was found to be kojic acid. This substance, 5-hydroxy-2-hydroxymethyl-8-pyrone, was present in the crude filtrates in a concentration of nearly one per cent. The high concentration accounted for the apparent high level of activity of the filtrates.

PROPERTIES OF KOJIC ACID

This material was first reported as a product of mold metabolism by Saito in 1907 (1). Kojic acid may be separated from filtrates by a method described

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[1] From The Children's Hospital of Philadelphia (Department of Pediatrics, University of Pennsylvania), the Henry Phipps Institute, Philadelphia, Pennsylvania, and the Heyden Chemical Corporation, Princeton, New Jersey.

[2] This study was supported by grants from the National Tuberculosis Association and the Committee on Advancement of Research of the University of Pennsylvania. The work on growth of the mold and preparation of filtrates was done by the Heyden Chemical Corporation.

[3] Mold observed and isolated by Dr. Max Lurie, 1947.

[4] The composition of the medium was as follows:

$NaNO_3$	3.0 Gm.
K_2HPO_4	1.0 Gm.
$MgSO_4 \cdot 7H_2O$	0.5 Gm.
KCl	0.5 Gm.
$FeSO_4 \cdot H_2O$	1.0 Gm.
Yeast Extract	1.0 Gm.
$CaCO_3$	10 Gm.
Dextrose	40 Gm.
Sucrose	100 Gm.
Water	1,000 ml.

by Birkinshaw (5). The filtrate volume is reduced by evaporation. This has been done at room temperature by evaporation from viscosine membrane in a moving air stream. The residual filtrate is chilled and crystals are separated by filtration. The crystals are dissolved in ethyl alcohol and an equal volume of ether is added. Any precipitate is removed by filtration. Part of the ether is distilled off and the kojic acid is crystallized from the hot alcohol residue. Yellowish-white crystals are obtained.

Kojic acid gives a reddish-purple color with ferric chloride reagent and the substance is most readily identified by spectrophotometry of this color in the visible range, as shown in figure 1. The maximum absorption is at 500 millimi-

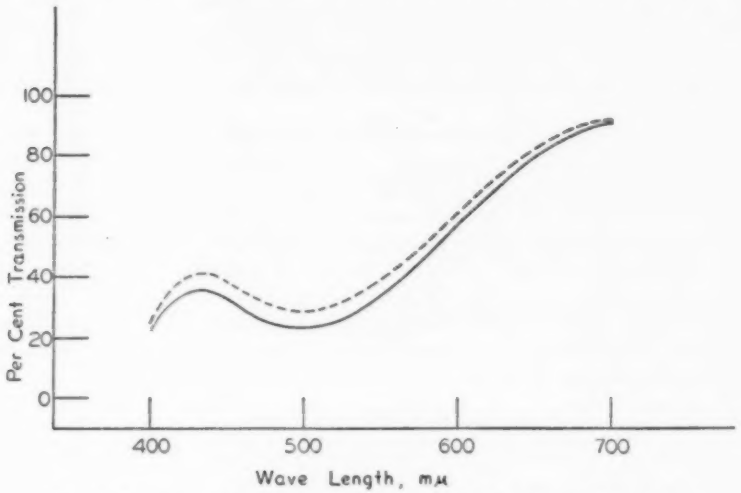

FIG. 1. Spectrographic absorption of ferric ion-kojic acid reaction product.

Dotted line = 1.00 mg. of kojic acid diluted to 10 ml. plus 5.00 ml. of 1 per cent ferric ammonium sulfate reagent.

Solid line = 0.112 Gm. of fermentation liquor diluted to 10 ml. plus 5.00 ml. of one per cent ferric ammonium sulfate reagent.

crons. Even as closely related a compound as maltol (2-methyl-3-hydroxypyrone) gives with ferric reagent a color in which the maximum is displaced 20 millimicrons toward the red end of the spectrum. It will be seen from the figure that the graph obtained by spectrophotometry of a fermentation broth is superimposable upon that obtained from pure kojic acid.

The list of fungi now known to be producers of kojic acid is currently as follows: *Aspergillus albus*, *A. awamori*, *A. candidus*, *A. clavatus*, *A. effusus*, *A. flavus*, *A. fumigatus*, *A. giganteus*, *A. gymnosardae*, *A. luteo-viriscens*, *A. nidulans*, *A. oryzae*, *A. parasiticus*, *A. tamarii*, and *Penicillium dalae*. Production of kojic acid has been recognized in commercial fermentative processes for many years (2).

ANTITUBERCULOUS ACTIVITY OF KOJIC ACID

The antibacterial spectrum of kojic acid has been reported, but there is an absence of data concerning its activity with reference to tubercle bacilli (4).

The present studies indicate that kojic acid is active against human tubercle bacilli under a variety of cultural conditions. Strains of mycobacteria tested were A-27 (human), avian 37, streptomycin-sensitive and streptomycin-resistant Ravenel, BCG, and *Mycobacterium phlei*. Details of testing the different strains varied slightly but all were inhibited by essentially the same concentrations. The presence of Tween 80 in media greatly favors the inhibitory effect.

Well-established surface growth on Long's liquid medium with or without 10 per cent serum is completely inhibited by 45 mg. of kojic acid per 100 cc. of medium. In subsurface cultures the amounts required for inhibition are somewhat less. Activity is not prevented by full strength defatted plasma on the surface of which A-27 bacilli can be grown after transfer from serum-containing liquid media.

Cultures on Long's medium which have been completely inhibited for a three weeks' period will in most instances grow out when transplanted to fresh media without kojic acid. The effect at inhibitory levels is, therefore, bacteriostatic and not bactericidal. It was also observed that growth resumes in inhibited cultures when the kojic acid is present at near threshold levels. Since the kojic acid is presumably stable under the conditions present, it is probable that resistant organisms grow out.

The amount of kojic acid required for tuberculostatic effect is very great as compared to many other substances, and its toxicity would have to be low to permit usefulness *in vivo*.

TOXICITY OF KOJIC ACID

Toxicity of kojic acid for mice was reported by Morton. By intraperitoneal injection the M.L.D. was found to be 187 mg. per 100 Gm. of mouse (4). Friedmann in 1934 reported the toxicity for dogs; 150 mg. per Kg. produced salivation, retching, vomiting, defecation, and somnolence. Convulsions followed larger doses. The M.L.D. for rabbits using the sodium salt was observed to be one Gm. per Kg.

When tested in the 12-day chick embryo, using solutions brought to pH 7 by addition of sodium hydroxide, the toxicity was found to be such that 12 mg. per 100 Gm. egg weight killed 100 per cent of the embryos. The L.D. 50 was approximately 6 mg. per 100 Gm. egg weight or 3 mg. per embryo.

The material was administered in physiologic saline solution via the surface of the exposed chorioallantoic membrane. This route has previously been shown to give good absorption of soluble materials (6). Many other substances have a higher tuberculostatic activity level and lower toxicity for embryos and, accordingly, chemotherapeutic experiments were not carried out.

COMMENT

Reports have appeared in the past few years of unidentified substances, active *in vitro* against tubercle bacilli, which have been present in filtrates prepared

from unidentified molds. Information given does not make it possible to eliminate kojic acid as the active substance.

The results of the present study indicate that kojic acid must be ruled out as a source of activity in mold products active *in vitro* against tubercle bacilli. The presence of this material can most readily be determined by spectrophotometry of its color reaction with ferric reagent.

Acknowledgment

The authors wish to express appreciation to Dr. Clark B. Bricker of the Department of Chemistry, Princeton University, for the spectrographic data.

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Case Reports

EMPHYSEMATOUS BULLA COMPLICATED BY HEMORRHAGE AND INFECTION[1,2]

Treated With Surgical Drainage

WILSON WEISEL AND IRVIN SLOTNIK

(Received for publication August 12, 1949)

The complex clinical picture produced by hemorrhage into, and secondary infection of, an emphysematous bulla, and the surgical treatment of these complications has prompted the following case report:

Case No. 105960. T.K., a 52-year-old white male was admitted to this hospital July 14, 1948 with the complaint of "shortness of breath." He stated that he had had a productive cough following an episode of influenza in 1918, which had gradually increased in severity and had been associated with a progressive shortness of breath on slight exertion for the past twenty years. He stated that ten years before entry his shortness of breath had become so disabling as to curtail markedly his activity and working potential. Four years previously he had contracted pneumonia. Following this episode he noted an increase in his dyspnea and was conscious of the fact that he was raising an average of two ounces of white-yellow, thick sputum daily.

In spite of the complaints enumerated, however, the patient was never completely incapacitated until ten days prior to admission. At this time he noted an increase in his shortness of breath which became so severe that he was confined to a chair existence, and for the first time was forced to sleep sitting up. A few days prior to admission he noted that he was coughing up a brown fluid which ceased about two days before admission, and with the disappearance of the brown sputum there was an accompanying increase in his dyspnea.

An evaluation of the patient's past history revealed that he had never had asthma, tuberculosis, rheumatic fever, heart disease, chest pain, ankle edema, nocturnal dyspnea, or hypertension. Review of the family history gave no evidence of familial diseases.

Physical examination on admission revealed a chronically ill, emaciated male in marked respiratory distress. His temperature was 100°F., the pulse rate was 102, and the respirations numbered 32 per minute. The accessory respiratory muscles were used constantly, and the patient's hands and face showed a moderate cyanosis. Examination of the chest revealed a hyper-resonant percussion note over most of the chest, except at the left base posteriorly where dullness was elicited. The breath sounds were decreased over the entire left chest and moist rales were heard over the right chest. Examination of the heart revealed a shift of the apex beat to the right of the left midclavicular line. The heart sounds, although rapid, were regular and of good quality. No heart murmurs were heard. The abdomen was scaphoid; the liver, kidneys, and spleen could not be felt and no masses were palpable in the abdomen. The extremities presented no edema; the deep tendon reflexes were physiologic, and no clubbing was noted of the fingers or toes.

The pertinent clinical findings on admission were a hemoglobin of 13 Gm. per 100 cc. of blood; a total leukocyte count of 26,200 per cu. mm. with a differential count of 86 per

[1] From the Departments of Surgery and Medicine, Veterans Administration Hospital, Wood, Wisconsin, and the Marquette University School of Medicine.

[2] Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author.

cent polymorphonuclear leukocytes, 5 per cent lymphocytes, and 9 per cent monocytes. A gram stain of the sputum showed gram-negative and -positive cocci. A roentgenogram of the chest revealed what was interpreted as a marked elevation of the left diaphragm with marked interstitial fibrotic changes in both right and left lung fields (figure 1).

The patient was given oxygen by BLB mask at a rate of eight liters per minute soon after his admission, with improvement in his color and a decrease in the respiratory rate. He was also started on parenteral penicillin, 80,000 units being given every four hours. On July 19, 1948 the patient's condition appeared to be worse in spite of the therapy mentioned. His temperature rose to 102°F., the respirations were markedly labored, and it was noted that very little sputum was being raised. A change also was noted in the physical examinations. The initially observed dullness at the left base was found to extend higher posteriorly and the entire left chest was hyper-resonant. Bronchial breath sounds with bronchophony

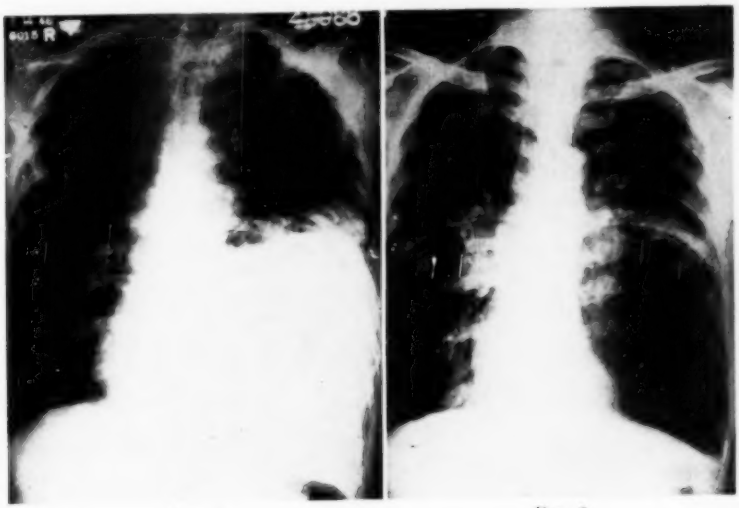

FIG. 1 FIG. 2

FIG. 1 (Left). Roentgenogram of the thorax, July 14, 1948, showing what was interpreted as marked elevation of the left diaphragm.

FIG. 2 (Right). Roentgenogram of thorax, February 20, 1943, revealing a large cystic area in the left lower lobe.

and pectoriloquy were heard at the left apex. Because of these changes, a further series of roentgenographic studies were performed.

It was apparent after the initial roentgenographic examinations that the findings of a high diaphragm were not consistent with the physical findings. It was believed that dullness and decreased breath sounds at the left base could not be explained by a high diaphragm. In addition it was noted that on percussion of the anterior chest the stomach tympany was at a normal level with the area of dullness extending well above the area of tympany. It was believed that these findings were indicative of an infrapulmonary effusion.

By fluoroscopy of the chest and abdomen the gastric air bubble was found to be widely separated from the upper level of the increased density noted in the left lower chest. The left diaphragm apparently moved in a normal manner, but there was no shift observed with change in position of the left chest density.

Because of the patient's persistent and increasing dyspnea, an aspiration of this apparent infrapulmonary effusion was deemed advisable. On July 20, 1948 the left chest was aspirated through the ninth interspace in the midaxillary line and 800 cc. of a bloody, brown, odorless fluid were removed. This procedure gave the patient a dramatic relief from his dyspnea. The fluid removed had a specific gravity of 1.025; 23 leukocytes were counted and, in spite of the grossly bloody character, no erythrocytes were seen; the protein content was 5 Gm. per 100 cc. No acid-fast bacilli and no tumor cells were seen on appropriately stained smears.

On the following day another 500 cc. of fluid similar to that described above were aspirated with further relief noted in the patient's symptoms. Following another aspiration of 250 cc., it was noted that the area of dullness at the left base corresponded to that observed on admission. From July 28 to August 13, 1948 three further aspirations were performed with the removal of 250 cc. of fluid on each occasion. Although there had been a marked improvement in his general condition, the patient continued to run a low-grade elevation of temperature from 99°F. to 100.4°F.; the penicillin therapy had been maintained and oxygen administration was constantly required.

At this period in the patient's hospitalization, roentgenograms of his chest which had been taken in 1943 were received from another institution. These revealed bilateral marked fibrosis and emphysematous changes. In addition, a large cystic area was seen in the base of the left lung which occupied the same area represented by the area of density or effusion previously described (figure 2). After viewing these films it was obvious that we were dealing with some type of pulmonary cyst with a superimposed hemorrhage into the cystic area.

The patient again began to pursue a downhill course, as evidenced by increased dyspnea, elevated temperature of a spiking type, inability to eat because of air hunger, and periods of marked mental torpor. These symptoms and findings coincided with a change in the character of fluid obtained by aspiration which became purulent in character. Because this poor clinical course persisted in spite of adequate penicillin and streptomycin therapy, it was deemed advisable to attempt surgical drainage of the cavity in spite of his grave condition.

On August 17, 1948 under local 1 per cent novocaine infiltration anesthesia, with the patient receiving 95 per cent oxygen by mask, a four-inch segment of the tenth rib was removed in the midaxillary line. After incision of the periosteal bed, pleural symphysis was found over the area of the bulla so that the incision was carried into the cavity. The cavity was filled with a foul-smelling caseous material with many areas of old blood clot. This material was removed with forceps and the suction tip. The wall of the cavity had a dirty, patchy, and purulent appearance. Running across the cavity was a large blood vessel which subtended the cavity as the diameter of a circle. This vessel was apparently thrombosed although, after ligation of the vessel with silk sutures at each extremity and severance with a cautery knife, it was found to contain liquid bloody material.

Within the cavity three small bronchial orifices could be seen protruding through the wall and these could be seen to bubble with expiratory phases of respiration. A large soft rubber tube was anchored to the opening in the chest wall for drainage of the cavity, and dressings were applied to the wound.

The patient's postoperative course was dramatic in that he had relief of his symptoms immediately after drainage of the infected bulla. On August 18, the day following his operation, his temperature was 98.6°F., the pulse rate was 74 beats per minute, and the respirations numbered 20 per minute. His respiratory effort and skin color had returned to normal, and he was able to rest in bed and to eat without oxygen therapy for the first time in three and one-half weeks.

Pathologic examination of material obtained by biopsies of the cyst wall at the time of thoracotomy were reported as showing granulation tissue and compressed pulmonary alveoli with superimposed hemorrhage and necrotic tissue. Examination of the necrotic contents of the cyst removed at operation revealed on smear a predominantly cellular character, 95 per cent of which were polymorphonuclear leukocytes and 5 per cent lympho-

cytes. No bacterial organisms were seen on the smear and no organisms were obtained by cultural methods.

The patient's clinical improvement continued and the cyst wall was cleansed daily with sterile gauze swabs and normal saline solution; the rubber tube drain was also cleansed and replaced daily. There was a gradual although slight reduction in the size of the cavity, but the character of the bulla wall changed from a grey, dirty, ragged appearance to a glistening pink-white wall.

Because of the patient's markedly decreased pulmonary reserve and because of electrocardiographic changes suggestive of coronary arterial disease, further radical surgery was deemed inadvisable. A revision of the thoracotomy wound was performed, however, on October 27, 1948, in order to remove an excess of granulation tissue and to enlarge the external chest opening.

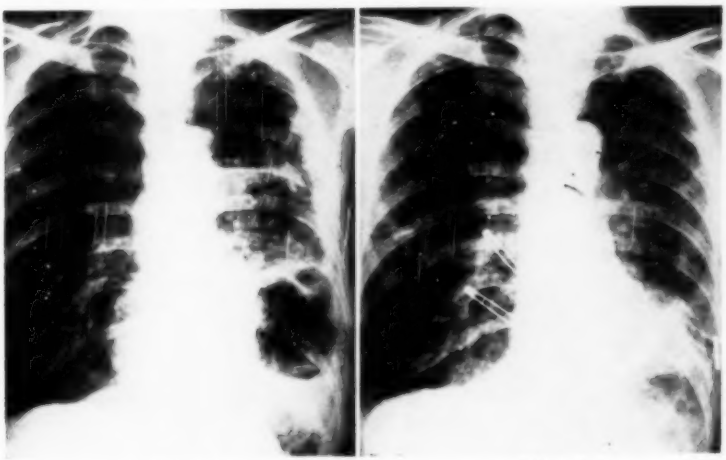

FIG. 3a FIG. 3b

FIG. 3a (Left). Postoperative roentgenogram of the thorax following surgical drainage of the infected bulla of the left lower lobe.

FIG. 3b (Right). Roentgenogram of chest, March 21, 1949, showing disappearance of previous cystic area and residual thickening of the pleura at operative site in left lower chest.

Since no further surgery was contemplated and his clinical improvement had continued, the patient was discharged from the hospital on January 21, 1949. At that time he was able to take care of himself and was ambulatory with only mild dyspnea. The bullous cavity was tubular in character and it measured 2.5 by 8 cm. A slight purulent type of discharge from the wound was noted and only a small bronchial communication within the cavity could be demonstrated. He was discharged to the care of his physician for dressings and continued care of the drainage tube.

The patient returned to this hospital for an evaluation examination on March 21, 1949. At that time a tract extending two inches below the skin surface and about one inch in diameter was still present. No evidence of cavity or bronchial communication could be determined. Roentgenographic examinations of the chest at this time revealed extensive fibrotic and slight emphysematous changes throughout both lungs. Complete disappearance of the previously demonstrated emphysematous bulla in the left lower lung field had occurred and a residual thickened pleura near the operative site was present (figure 3).

The only complaint of the patient was moderate dyspnea on moderate exertion. Because of these findings the drainage tube was removed and the sinus tract was allowed to close by granulation tissue and secondary cicatrix.

DISCUSSION

The subject of cystic disease of the lung has been one of interest, conjecture, and controversy in the past, and there are as yet many features of its development, pathogenesis, and treatment which are not completely understood. In this discussion, however, we have utilized Miller's (3, 4) definition of a bulla as an area of vesicular emphysema within the lung substance. It was believed that a congenital type of cyst apparently could be disregarded in this patient on the basis of the clinical course and the lack of an epithelial lining in the pathologic studies of the cyst wall.

The history in this patient of acute and chronic pulmonary infection probably was a factor in the development of the cavity seen, and the factors which caused its persistence were probably complex, as has been emphasized by Maier (1).

The case we have presented has been of particular interest because of the unusual roentgenographic features produced by hemorrhage into the bullous cavity, the initial picture simulating an elevated left diaphragm, or the so-called infrapulmonary effusion (6). In fact, the true nature of the process was not clear until previous roentgenograms showing the bulla were reviewed, and from a diagnostic viewpoint this case presented problems similar to those cases of infected epithelialized cysts reported by Maier and Haight (2).

The surgical drainage in this case produced a dramatic clinical response and led to eventual disappearance of the cyst without more extensive surgery such as that described by Naclerio and Langer (5).

SUMMARY

A case of an emphysematous bulla occurring in a 52-year-old white male is presented, which caused a complex clinical picture because of hemorrhage into the cavity with secondary infection of the bulla. The infected bulla was treated by surgical drainage with recovery of the patient and apparent disappearance of the bulla.

SUMARIO

Bula Enfisematosa Complicada por Hemorragia e Infección: Tratamiento por la Canalización Quirúrgica

Este caso de bula enfisematosa en un sujeto blanco de 54 años de edad ocasionó un cuadro clínico complejo, debido a una hemorragia en la cavidad con infección secundaria de la bula. La bula infectada fué tratada con la canalización cruenta, reponiéndose el enfermo y desapareciendo aparentemente la bula.

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STREPTOMYCIN AND PROMIZOLE IN THE TREATMENT OF WIDESPREAD PULMONARY TUBERCULOSIS IN A 19-DAY-OLD INFANT[1]

Case Report

EDWIN L. KENDIG, JR. AND FRANKLIN L. ANGELL

(Received for publication October 13, 1949)

Since all studies concerning the use of streptomycin and other drugs in the treatment of miliary tuberculosis and tuberculous meningitis are necessarily incomplete, it would seem that the report of apparently successful treatment of widespread pulmonary tuberculosis in a 19-day-old infant is of importance.

CASE REPORT

At 2 p.m. on August 2, 1948, R. K., a 2,268-gram Negro female, was admitted to Dooley Hospital. She was born at home without benefit of attendance ten hours prior to admission. The mother, who is known to have tuberculosis with sputum positive for tubercle bacilli, stated that the baby was "born into the toilet." The baby was kept on the dressing table about 10 to 12 feet away from the mother until both were brought in the same ambulance to the hospital. The mother was admitted to St. Phillip's Hospital for a sterilization procedure.

Physical examination at the time of admission revealed an apparently normal premature infant, who weighed 2,268 Gm.

The infant showed the usual physiologic weight loss, but by 19 days of age had begun gaining nicely and weighed 2,211 Gm. At that time a rectal temperature elevation of 100.8°F. was noted. Physical examination was essentially negative except for mild dehydration.

In view of the mother's tuberculosis history, a roentgenogram of the infant's chest was obtained. According to the chief radiologist, this film (taken when the child was 19 days of age) showed "very fine miliary mottling throughout both lungs." A Mantoux test, in dilution of 0.001 mg., was done the same day, and the reaction was positive. On August 25, 1948, when the patient was 23 days old, intramuscular streptomycin in dosage of 150 mg. daily was begun and the next day the dosage was doubled. When the baby was 25 days old, tubercle bacilli were demonstrated by direct smear and culture of gastric contents.

On the next day the cerebrospinal fluid examination showed 15 cells, with 11 lymphocytes and 4 polymorphonuclears. The cerebrospinal fluid protein was 104 mg. per 100 cc., the sugar was 46 mg. per 100 cc., and the chlorides were 89 milliequivalents per liter. No acid-fast organisms were isolated by smear, culture, or guinea pig inoculation from this or any other cerebrospinal fluid examination. Streptomycin, 25 mg. intrathecally every two days, was instituted. During the course of intrathecal streptomycin therapy, which lasted for approximately three months, the maximum cerebrospinal fluid cell count was 50 cells, with 29 polymorphonuclears and 21 lymphocytes. Nine days following discontinuation of intrathecal therapy, examination of the fluid revealed no cells. During this period intramuscular administration of streptomycin was continued in dosage of 30 to 40 mg. per pound of body weight. The last cerebrospinal fluid examination on July 28, 1949 showed only one cell and a normal protein.

The patient's fever reached a maximum of 105°F. (rectal) on August 29, 1948 when she was 27 days old, and subsided to normal six days later. After that time there were two transient elevations of temperature, apparently caused by acute upper respiratory infections and controlled by means of penicillin therapy.

[1] From the Department of Pediatrics, Medical College of Virginia, Richmond, Virginia.

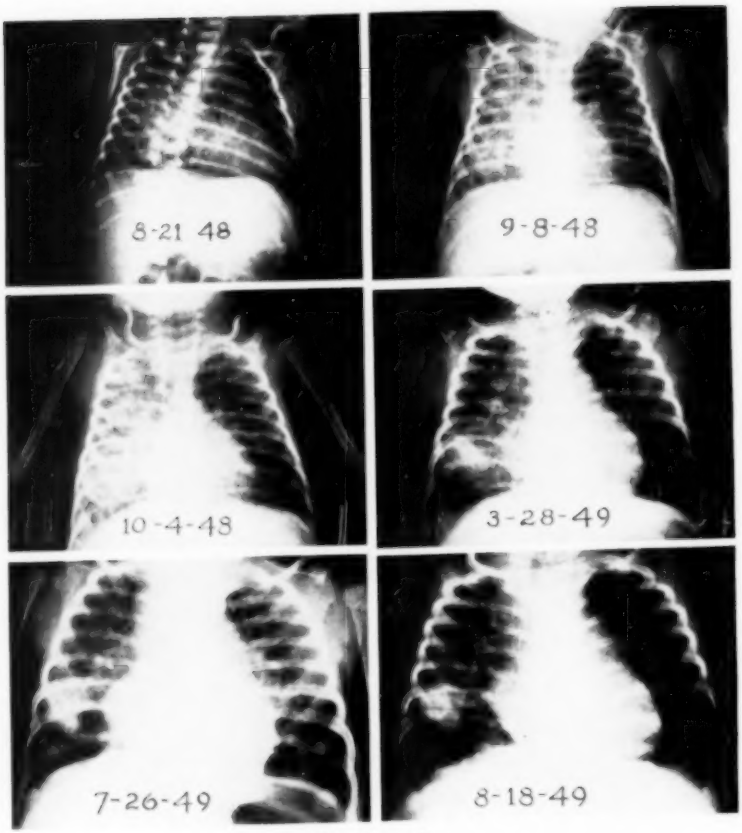

FIG. 1(a to f)

(Upper left) Initial roentgenogram, August 21, 1948, showing very fine miliary mottling throughout both lungs.

(Upper right) Roentgenogram, September 8, 1948, showing increase in mottling of lungs, more conglomerate and extensive in right lung.

(Center left) Roentgenogram, October 4, 1948, showing increase in mottling of lungs, more conglomerate and extensive in right lung.

(Center right) Roentgenogram, March 28, 1949, showing diminution in left lung densities with additional fibrosis of the entire right hilum and inner trunk regions merging with the Ghon complex.

(Lower left) Roentgenogram, July 26, 1949.

(Lower right) Roentgenogram, August 18, 1949, showing the right healed primary focus 1.5 cm. in measurement. Right linear fibrosis with the slightest nodularity persisted. The left lung was clear.

When the baby was 4 months old, streptomycin was temporarily discontinued and Promizole was begun in dosage sufficient to maintain a serum concentration of 2 to 3 mg. per 100 cc. When the patient had an elevation of temperature (acute upper respiratory infection) one month later, streptomycin therapy was again instituted and continued until

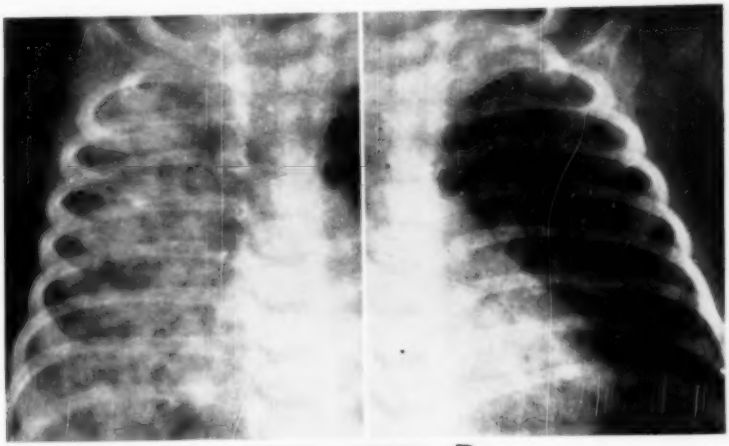

FIG. 2a. (Left) Roentgenogram, October 4, 1948, right lung. Magnified 1.5×
FIG. 2b. (Right) Roentgenogram, October 4, 1948, left lung. Magnified 1.5×
FIG. 3 (Bottom) R. K. at 12 months of age

the baby was 12 months old, except for one 2-month period during which dihydrostreptomycin was substituted. The patient is still receiving Promizole therapy.

When the baby was 2 months of age she weighed 2,665 Gm. and one month later 3,182 Gm. On August 12, 1949, when slightly more than one year of age, she weighed 6,804 Gm. At that time she appeared to be retarded in development in that she could neither sit alone nor stand, but it must be stated that she had been given no opportunity to learn to do so. She appears to be normally alert.

INTERPRETATION OF ROENTGENOGRAMS

A review of the roentgenograms by Dr. F. B. Mandeville, Chief Radiologist, was as follows:

During a period of one year, from August 21, 1948 through August 18, 1949, fourteen roentgenographic examinations of the chest were made.

The initial chest film on August 21, 1948 showed very fine miliary mottling throughout both lungs.

Additional examinations on September 8, October 4, and October 30, 1948 suggested an increase in the mottling of the lungs, always more conglomerate and extensive in the right lung.

The film of November 29, 1948 showed a diminution in the mottling in the right lung, with conglomerate right hilar nodes persisting along with the mottling of the left lung.

On December 23, 1948 the film showed an oval nodule 1.5 cm. in diameter in the periphery of the right lung between the seventh and eighth ribs as measured posteriorly, with right hilar nodules. This suggested a well-defined Ghon complex. The mottling showed evidence of further diminution with clearing and remarkable improvement in both lungs.

On January 10, 1949 the Ghon complex was well defined with linear fibrous densities suggested in both hilar and trunk densities.

The film of March 28, 1949 showed diminution in left lung densities with additional fibrosis of the entire right hilum and inner trunk regions merging with the Ghon complex.

By April 28, 1949 roentgenographic examination suggested further disappearance of any mottling and clearing of the linear fibrous densities so prominent in the two previous examinations.

The film of August 18, 1949 showed the right healed primary focus 1.5 cm. in diameter and a group of right hilar nodes 1.5 by 3 cm. in measurement. Right linear fibrosis with the slightest nodularity persisted. The left lung was clear.

COMMENT

As far as we can determine, this is the youngest recorded case of widespread pulmonary tuberculosis with recovery. It is not suggested that this case is of congenital origin. Without evidence of placental involvement, this could not be proved. Moreover, roentgenograms of the chest show the presence of a parenchymal lesion which must be considered to be part of the so-called primary complex. This finding would suggest that the baby either aspirated tuberculous amniotic fluid or was infected by the mother during the brief 10-hour contact immediately following birth.

The question of possible tuberculous meningitis must be raised. The original cerebrospinal fluid examination revealed 15 white blood cells per cu. mm. and a total protein 104 mg. per 100 cc. While these findings suggest tuberculous meningitis, failure to isolate the tubercle bacillus by either smear, culture, or guinea pig inoculation precluded the establishment of such a diagnosis.

Addendum

At 19 months of age the patient shows no clinical sign of active tuberculous infection.

Acknowledgment

The authors are grateful to Dr. F. B. Mandeville for his review and interpretation of the roentgenograms.

Editorial

Scientific Appraisement of New Drugs in Tuberculosis

The advent of chemotherapy in tuberculosis has changed our approach to treatment in unexpected ways. The recent discoveries in this field, in an era when effective rapid therapy of many other diseases has been found, led many to expect similarly complete solutions to our tuberculosis problems. Indeed, the cure of some patients with acute miliary and meningeal tuberculosis, even though many others do not respond, was a striking achievement, and encouraged a belief, against all reason, that similar results might obtain in other forms of the disease. We have learned our lesson and, though in the space of a very few years much of our treatment of the less fulminating forms of tuberculosis has altered, thanks to the additional assistance given by streptomycin, we have become aware of the limitations not only of streptomycin but of possibly all chemotherapy in tuberculosis.

The development of caution in our expectation of results has gone hand in hand with the development of a cool skepticism concerning the results obtained. While the clear analytical eye was once a rare phenomenon, and new treatments were often hailed almost at sight on the bona fide of a single observer (and still are in many parts of the world), recently the number of medical men who have revolted against the erratic empiricism of former years has multiplied exceedingly. In no field of work was this more necessary than in tuberculosis, most unpredictable of diseases. It is now becoming generally accepted that scientific appraisement of new drugs in tuberculosis is a fundamental necessity, but it is hard to realize that this particular progress has been made almost entirely within the past five years. In May 1944 Hinshaw and Feldman, at the 40th Annual Meeting of the National Tuberculosis Association, presented a suggested procedure for the evaluation of chemotherapeutic agents in clinical tuberculosis, following their analysis of the inconclusive results of treatment with sulfone drugs. They concluded that "The acceptance or rejection of chemotherapeutic agents, which may be proposed for the treatment of tuberculosis, must depend on experimental and clinical studies which have been rigidly controlled and accurately recorded." Though the report on streptomycin which they published a year later (Proc. Staff Meet., Mayo Clin., 1945, *20*, 313) related to an uncontrolled clinical trial, the results were sufficiently promising to warrant the inception of clinical trials of the type they had proposed, and a series of large scale investigations followed, designed to appraise scientifically the effects of streptomycin therapy.

Until recently investigations of this type were confined to the United States and Great Britain. In the first trial by the Veterans Administration, the results of streptomycin treatment in 286 cases of pulmonary tuberculosis were assessed by comparing the pretreatment course of the disease with the course during treatment, the roentgenograms being reviewed by an impartial jury (J. A. M. A., 1948, *138*, 584). The British Medical Research Council, in the autumn of 1946,

organized a controlled trial of streptomycin in pulmonary tuberculosis and reported its results in October 1948 (Brit. M. J., 1948, *2*, 769). A control study by the Tuberculosis Study Section of the National Institutes of Health (Public Health Service) was begun in 1947. Both of these control studies involved a comparison of results in a group treated with streptomycin with those in a group not receiving streptomycin but otherwise similarly treated; allocation to one or the other group was by random selection. In the British study a severe type of disease unsuitable for collapse therapy was chosen and bed rest was the only other treatment given; in the United States study other forms of treatment were given in both groups. At the same time comparative regimen investigations were undertaken by the N. I. H. Tuberculosis Study Section and the Veterans Administration, and later by the Medical Research Council. These trials have demonstrated clearly that, given adequate preliminary planning of the investigation, an unequivocal answer can be obtained in a relatively short space of time. In the first Medical Research Council streptomycin trial the time involved was less than two years, and a shorter period was involved in a trial of PAS now terminated. When one compares these results with the many years of inconclusive work on gold therapy, there can be little doubt about the relative rapidity and economy of the method. It has been applied to new advances in chemotherapy; one wonders what would be the status of other tuberculosis treatment (bed rest and the various forms of collapse therapy) had such standards been applied long ago.

A feature of these recent developments, as important as the results obtained, is that the method has become so acceptable that many clinicians who previously worked independently, each within his hospital center, have been willing to merge their individuality sufficiently to take part in group investigations. To accept only patients approved by an independent team, to conform to an agreed plan of treatment, and to submit results for analysis by an outside investigator involves a considerable sacrifice, and this sacrifice is being made by an increasing number of physicians.

The Swedish trial of PAS reported in this issue of the REVIEW is, to our knowledge, the first controlled trial in a country other than the United States and Great Britain. It is a particular credit to the clinicians concerned that it was undertaken in the country where the value of PAS was first discovered, and at a time when the drug was freely available and its clinical effectiveness was being widely proclaimed. In fact, unfortunately, premature publicity in the Swedish press had led in 1947 to criticism of the existing evidence by Hedvall and Heimbeck (in discussion of a paper by Alin and Difs, Nord. Med., 1947, *33*, 151), who contrasted the "meager results" with the descriptions given by the press. The authors of the present report say that the previously published observations gave "no direct information as to how large a part of the noted improvement could be ascribed to PAS, and how large a part was due to other treatment given at the same time." (How true this can be has been seen repeatedly in the Medical Research Council trials; some of the control patients, chosen like others as having rapidly progressive, bilateral pulmonary tuberculosis, improved when

treated by bed rest alone; others, selected on the same basis, had by the time of their admission made such good progress while waiting at home that they were no longer suitable for the trial.) The suggestive but inconclusive nature of the evidence concerning PAS led thus to the organization of controlled trials of this compound by the Therapeutic Trials Committee of the Swedish National Association against Tuberculosis, by the Veterans Administration in the United States, and by the M. R. C. Medical Research Unit with the cooperation of the Tuberculosis Association in Great Britain.

The Swedish trial has the essential features of a controlled investigation and is the work of physicians at five separate centers working in collaboration. They present an analysis of the results in 94 patients treated with PAS, and 82 "controls" treated without PAS but given a placebo of the same appearance and taste as PAS. The roentgenographic assessments were made by clinicians not in charge of the patients concerned. After a full use of statistical analysis of differences, the authors declare their results to be unequivocally in favor of PAS. The differences in the course of temperature, sedimentation rate, weight, and sputum are demonstrated; the results are indeed striking, and, added to the information collected elsewhere, lead to definite conclusions concerning the value of PAS.

Some essential details are omitted from the report, possibly because of required brevity. This leads one to consider if it is possible, in planning a trial, in reporting the results, or in assessing the published reports of trials, to apply criteria which must be satisfied if the analysis is to be entirely acceptable. Any criteria one attempts to formulate must not ignore the many difficulties besetting scientific investigations involving human beings; Walker and Barnwell, from their Veterans Administration experience, have well described these limitations (Ann. New York Acad. Sc., 1949, *52*, 742). A high standard must be set, however, not only in order to assess the validity of the results, but also because pioneering investigations of this type may in many ways serve as a model and lesson to future investigators. A basic principle one can set up is that, just as in a laboratory experiment report, it is at least as important to describe the techniques employed and the conditions in which the investigation was conducted, as to give the detailed statistical analysis of results. One must know, for instance, how cases are selected for the trial; if the trial is concerned with pulmonary tuberculosis, what type of disease makes patients qualify from among the many hundreds of patients available. If cases are allotted to a control group or to a treatment group, or to one of several treatment groups, what method of random selection is used? With what frequency are routine examinations made? Are all cases bacteriologically confirmed, and what are the criteria of a "negative" sputum test? The dosage and duration of treatment, the numbers given collapse therapy in each group, must be stated. The roentgenographic assessment must have been made by an independent panel and after equivalent periods of observation or treatment in each group. It is essential also that all cases be accounted for; a large percentage unexamined leaves too many open questions.

These are some features of the background information required. The Swedish

report provides much of it, and, though there are still many questions that one would wish to put regarding such a trial, it has certainly established that PAS is effective in certain forms of tuberculosis. How effective PAS is and how it can best be combined with other forms of therapy cannot be clearly stated at this juncture, nor indeed can these questions be entirely answered for streptomycin. The preparation of patients for collapse therapy, the administration of one drug to patients whose bacilli are resistant to another, the treatment of early minimal lesions, the treatment of patients at home while waiting for admission to hospital (a sore problem in Great Britain) are only a few of the possibilities. Most important is the question of drug resistance. This subject is not covered in the Swedish report, but there is gathering evidence that PAS resistance is seen relatively seldom. This leads us to the important consideration: Can the emergence of streptomycin resistance be delayed or prevented by association with PAS? By the method of comparative regimen trials designed in the same way as the controlled investigations, the answer to this question has been reached on both sides of the Atlantic: by the V.A. trials in the United States, and by the M.R.C. trials in Great Britain. Here again, thanks to the planning of these investigations, it has been possible to get an unequivocal answer in a relatively short space of time. In the British trial, with groups of over 50 patients each, all chosen as having a similar type of disease, it was found that streptomycin resistance emerged much less often in patients treated with PAS and streptomycin than in those treated with streptomycin alone; the results obtained before the trial had ended were considered important and decisive enough to warrant an interim communication (Brit. M. J., Dec. 31, 1949, p. 1521).

These results are a rich reward for the total cooperative effort of many scores of clinicians and bacteriologists working on these problems. Many questions remain to be answered and no doubt by such methods some of them can be clearly answered, though we must remember that usually these trials cover limited types of disease, and that the replies to some questions concerning the most effective and timely uses of chemotherapy can only be obtained from the cumulative experience of individual clinicians. But with each result achieved, the problems and the methods required to solve them must change. The problems of trial of a new chemotherapeutic agent in tuberculosis now are very different from those which confronted us when investigating streptomycin for the first time. The original controlled streptomycin trial was possible because of shortage of the drug; the trials of PAS were undertaken at a time when PAS was generally available, and (in Great Britain) at the request of the Ministry of Health and representatives of the clinicians unable to decide on the conflicting evidence. The problems of trial vary with availability of the drug in question; they are different also for different forms of the disease. First, in the rapidly fatal forms of tuberculosis, obviously no control is necessary but, since the effectiveness of streptomycin has been demonstrated in a proportion of cases, it is difficult to withhold streptomycin and try a new drug (incidentally it is interesting that PAS is not effective in these conditions, though one would expect the lesions of

acute miliary tuberculosis to be most amenable to effective chemotherapy). Secondly, in tuberculosis of the mucous membranes and in draining cutaneous sinuses, it may be possible to reach a fair conclusion on treated cases alone. Thus Hinshaw and McDermott (Am. Rev. Tuberc., 1950, *61*, 145), reviewing the evidence of the effect of thiosemicarbazone in tuberculous laryngitis, concluded that the results constitute acceptable evidence that the drug has a definite effect on tuberculosis. Thirdly, in the early minimal lesions of tuberculosis, there is room for trial of new drugs, since we are still in some doubt whether streptomycin treatment can be rendered so inocuous as to justify its use in this way on a large scale, and since the effective rapid treatment of early lesions would solve much of our tuberculosis problem. In order to reach a conclusion, however, any such trial must be fully controlled, with large numbers and a long follow-up, in view of the frequency of spontaneous regression of minimal lesions. Finally, in other forms of tuberculosis, where controlled trial is desirable and where the effect of streptomycin is less dramatic but nevertheless proved, one can no longer withhold chemotherapy entirely for a control group. If the drug is promising enough, streptomycin may be withheld and the new drug given instead. This was the position with PAS. In the British trial a group treated with this drug has been compared with a group treated with streptomycin. In the United States, trial of PAS alone was undertaken by the VA for patients with infections resistant to streptomycin, and the same policy has been adopted for the trial of thiosemicarbazone.

The report of this latter drug by Hinshaw and McDermott illustrates remarkably the difficulties of evaluation of a new drug in the absence of a planned investigation. As independent observers, reviewing evidence in more than 1,000 patients, they found it impossible to reach hard and fast conclusions regarding the drug's effect in pulmonary tuberculosis: "There was no question concerning the fact that the patients had attained excellent results, but it was not possible to relate the results with absolute certainty to the administration of Conteben. About the most that can be said is that these particular types of observations were 'suggestive' of some drug effect." Among the proposals they make is that studies should be directed toward determination if Conteben will delay the emergence of streptomycin-resistant tubercle bacilli when administered concurrently with streptomycin. Therein lies a method of assessment which has already shown its value in the trials of PAS. (It is interesting that in the VA trial, Promizole had no such effect.) The method is applicable and useful for drugs thought to be effective but definitely less so than streptomycin; this has been the position for PAS and for the thiosemicarbazones. We have not yet been faced with the problem of assessing a drug possibly more powerful than streptomycin. In that event scientific appraisement will still be indispensable, but a different approach will be needed.

Each advance made in chemotherapy tightens our criteria of evaluation and makes us more critical in our analysis of further advances, since new drugs must now be measured against those already proved effective. From the situation a

few years ago, when no specific chemotherapy for tuberculosis was known, the problem is unexpectedly becoming one of a choice of the most effective single drug, or the most effective combination of drugs. And this, in its turn, is only a part of the much larger problem which is the proper integration of chemotherapy within the whole plan of tuberculosis treatment.

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BOOKS

S. Di Rienzo: Radiologic Exploration of the Bronchus. Pp. 332, Charles C Thomas, Springfield, Illinois, 1949, Price $10.75.

Di Rienzo's book should be of particular interest to all radiologists, thoracic surgeons, phthisiologists, and others interested in diseases of the chest. Perhaps the most interesting portions of the book are those that deal with the physiology of the bronchus in its normal and diseased state. It has long been well known that there are changes in the diameter of the bronchi during respiration and cough; clear and graphic illustrations of these changes are demonstrated. In addition to a change in size, the author states that peristalsis occurs in the bronchus as it is known to occur in the gastrointestinal and urinary tracts. The presence and function of the muscular layer of the bronchi and bronchioles is repeatedly discussed and emphasized. Another very interesting concept is that of the "filling rhythm." It is stated that the sequence and rapidity with which the segments fill with the contrast substance is of diagnostic significance. One of his criteria for an asthmatic is that there is a delay in the progression of oil and that there is a lack of foliage. This feature of course cannot be appreciated in conventional film studies.

After preliminary chapters on the embryology, histology, anatomy, and characteristics of the bronchus, the author then discusses the alterations in the anatomy of the bronchus in bronchopulmonary malformations, bronchiectasis, emphysema, asthma, carcinoma, hydatidosis, and lung suppuration. Chapters are devoted to the technique of bronchography and to tomography. The chapter on bronchographic exploration in carcinoma was especially interesting. It would seem that a more extensive use of bronchography would be of value in cases of carcinoma, especially in those cases that cannot be visualized by bronchoscopy. The author devotes an entire chapter to the changes associated with hydatid cyst of the lung, apparently indicating the relative importance of this disease in his country.

There are many good illustrations. They have been reproduced as negatives, but since most of the reproductions are bronchograms, this is pleasing, as the bronchial tree stands out in black in sharp contrast to surrounding lung.

From a radiologic point of view, one of the important concepts to be gained is that a complete study of the bronchus includes fluoroscopic examination, and, if necessary, serial spot films during and after the instillation of contrast media.

L. B. Snow

Vinta Merrill: Atlas of Roentgenographic Positions. Pp. 664, Two volumes, with illustrations, The C. V. Mosby Co., St. Louis, 1949, Price $30.00.

The *Atlas of Roentgenographic Positions* was written by Vinta Merrill while she was Educational Director of Picker X-ray Corporation to provide a practical

reference book for X-ray technicians. Years of personal experience and research in this field plus intelligent planning were combined by the author to produce a fine book. The Atlas is written in a clear, concise manner and is profusely illustrated. It is a compilation of the standard, general roentgenographic positions, as well as many of the more practical, specialized positions. In addition, there is a great amount of general information for the technician, such as a brief, but adequate, discussion regarding general roentgenographic technique and the handling of patients.

The book is divided into chapters on the basis of anatomic regions. Each of the sections, such as the upper extremity, is introduced by a concise review of the anatomy of the part with illustrated drawings. In the chapters devoted to the study of internal organs, a short discussion of the physiology is also presented. As each roentgenographic position is introduced, an instruction is presented on how to place the patient and on the structures visualized in the position, while, on the same page, well-chosen photographs show the actual position of the part, the tube position, and an example of the resultant roentgenogram. No exposure factors are given. Although there is no information in this book regarding such special techniques as planigraphy and foreign body localization procedures, the Atlas, on the whole, is remarkably complete.

Included in this Atlas at the end of Volume I is a glossary of common anatomic and medical terms with which all technicians should be familiar. An excellent bibliography, carefully classified, together with a complete index of the work, is present at the end of each volume. The volumes are beautifully bound and printed and the general format is logical and pleasing to the eye. The Atlas is the best book of its kind published today, and a reference book to which every roentgen department can turn for practical information regarding almost any aspect of roentgenographic positioning.

DAVID R. HARRINGTON

A. P. Bertwistle: A Descriptive Atlas of Radiographs, an Aid to Modern Clinical Methods. Seventh edition, revised and enlarged, pp. 622, with 980 illustrations, The C. V. Mosby Co., St. Louis, 1949, Price $16.00.

The number of editions and reprintings of any medical text may probably be considered a satisfactory index of the nature of the reception tendered it by the profession. By this standard, if by none other, Mr. Bertwistle's atlas must of necessity be considered a valuable contribution, having now reached its seventh edition since its first appearance some twenty-three years ago.

However, many, if not most, of the errors of omission and commission first pointed out at that time continue to make themselves manifest, despite the revision and enlargement of the present edition. All of the illustrations (of which there are 980) are of the less desirable reversal type, and the quality of many of them is so poor that the detection of the pathology described is a virtual impossibility. Accompanying many of the illustrative roentgenograms are diagrammatic representations of them, some of these attaining the fantastically minis-

cule size of one centimeter square. The lettering of these diagrams continues to be proportionately microscopic and illegible.

A rather excellent section (which comprises about 90 per cent of the small amount of actual text) on "Milestones in Radio-diagnosis" is the main redeeming feature of the book. The attractiveness of this is lessened, however, by carelessness in editing and proofreading, so that numerous mistakes in spelling are obvious. Many prominent American radiologists may experience difficulty in realizing that specific references are directed to their work because of the incorrect and various ways in which their names are spelled.

Mr. Bertwistle continues to stress the supposedly great advantages of the "silhouette technic" (whereby the soft tissue outline is scratched on the film and everything outside of it blackened with india ink), and a considerable number of the illustrations are presented in this fashion. The annoying feature of printing radiographs without regard to topographic anatomy is still present. In some illustrations, the heart or stomach is on the left, in others on the right; the same is true for the gall bladder and other unilateral structures.

The introduction would benefit by revision, viz., the opening anachronistic statement: "The object of this book is to show the immense possibilities of X-rays."

In all fairness, the book is neither written by a radiologist nor intended for such an audience. Notwithstanding this fact, it would seem logical to expect a book on any subject to be more than merely a source of illustrative examples with which rather dangerous comparisons may be made. If this is the real purpose of this book, the price seems rather high for such an exercise.

BERNARD P. ADELMAN

AMERICAN TRUDEAU SOCIETY

Medical Section of the National Tuberculosis Association

Report of the Subcommittee on Clinical Classification of the Committee on Revision of Diagnostic Standards

DR. JOHN D. STEELE, *Chairman*

DR. ROBERT J. ANDERSON
DR. HOWARD W. BOSWORTH
DR. RALPH HORTON
DR. CARL MUSCHENHEIM
DR. J. N. WILSON
DR. JOHN B. BARNWELL

The following revisions are intended to replace *Extent of Pulmonary Lesions* (Item 5, page 20) and *Clinical Status* (Item 14, page 21) in the 1940 edition of *Diagnostic Standards.*

CLASSIFICATION OF PULMONARY TUBERCULOSIS

EXTENT OF PULMONARY LESIONS

Minimal: Slight lesions without demonstrable excavation confined to a small part of one or both lungs. The total extent of the lesions, regardless of distribution, shall not exceed the equivalent of the volume of lung tissue which lies above the second chondrosternal junction and the spine of the fourth or body of the fifth thoracic vertebra on one side.

Moderately advanced: One or both lungs may be involved, but the total extent of the lesions shall not exceed the following limits:

Slight disseminated lesions which may extend through not more than the volume of one lung, or the equivalent of this in both lungs.

Dense and confluent lesions which may extend through not more than the equivalent of one-third the volume of one lung.

Any gradation within the above limits.

Total diameter of cavities, if present, estimated not to exceed 4 cm.

Far advanced: Lesions more extensive than moderately advanced.

In the case of temporary collapse the extent of disease existing immediately before the collapse shall be continued in the classification until re-expansion permits reclassification.

In the case of permanent collapse or pulmonary excision, the extent of disease in a lung existing immediately before excision or collapse shall be continued in this classification through life, except that such extension or new deposits of disease as appear any time postoperatively in this or the contralateral lung shall be additions to the preoperative classification.

The form, site, and duration of the procedure shall be added in parenthesis to the classification of extent of disease.

In other cases the classification of extent will be changed as the change in the extent of the demonstrable lesion warrants. Once the diagnosis of pulmonary tuberculosis has been established, however, the extent of the lesion cannot be classified as less than minimal even when clearing on the roentgenogram appears to be complete.

It may be useful to classify the extent of lesions in each lung separately. When this is done, however, the combined extent for both lungs should always be designated.

The location of lesions may be further designated by bronchopulmonary segments. The terminology and classification of bronchopulmonary segments as suggested by Jackson and Huber (Gray's Anatomy, 25th Edition pp. 1134–1135) has been adopted as the official classification by the National Tuberculosis Association upon the recommendation of the American Association for Thoracic Surgery.

CLINICAL CLASSIFICATION

The following definitions, subject to the interpretation of the physician, apply regardless of the type of treatment given. Collapse therapy or pulmonary excision in effect at the time of classification will be indicated under extent of pulmonary lesions. The status of activity of lesions from a roentgenologic, symptomatic, and laboratory standpoint is first designated; the status of a patient in terms of exercise shall be designated next.

Roentgenologic, Symptomatic, and Laboratory Status

Inactive

The appearance of lesions by serial roentgenograms must be stable except for extremely slow shrinkage and there must be no roentgenologic evidence of cavity. Symptoms of tuberculous origin must be absent. Sputum, if any, must be found negative for tubercle bacilli repeatedly, not only by concentration and microscopic examination, but also by culture or animal inoculation.

When a patient is not raising sputum or when there is any question as to the authenticity or adequacy of expectorated sputum specimens, the fasting gastric contents or pulmonary secretions which have been aspirated from the tracheobronchial tree should be examined by culture or animal inoculation[1]. These conditions shall have existed at least six months. The period of inactivity shall be designated, if known; for example, Inactive (6 months), Inactive (1 year), Inactive (2 years), et cetera.

Arrested

The symptomatic and roentgenologic requirements of this group are the same as for "inactive." When sputum specimens or gastric contents have been found negative only by microscopic examination of concentrates and not by culture or animal inoculation, such patients cannot be classified "inactive." They may be classified "arrested" even though culture or animal inoculation may be positive and, among many concentrated specimens of sputum examined microscopically, an occasional positive may be found. These conditions shall have existed at least three months. The period of arrest shall be designated, if known; for example, Arrested (6 months), Arrested (1 year), Arrested (2 years), et cetera.

Active

Lesions may be stationary, retrogressive, or progressive, according to examination of serial roentgenograms. Symptoms of tuberculous origin may be present or may have been present recently. Sputum and gastric contents almost always contain tubercle bacilli,

[1] In a tuberculous patient no specified number of negative examinations gives absolute assurance that another specimen may not show tubercle bacilli. Nevertheless, it is convenient to designate an arbitrary number of negative examinations which may be taken as presumptive evidence of bacteriologic remission. It is recommended that three adequate specimens, taken at least a week apart, be found negative by culture or by animal inoculation.

although in some instances tubercle bacilli cannot be demonstrated even after repeated cultures and animal innoculations. The period of activity should be designated, if known; for example, Active (17 months), Active (3 years). The designations Active, *Improved*, or Active, *Unimproved*, may be used after an adequate period of observation or treatment.

Activity Undetermined

When activity has not been determined from adequate roentgenologic and laboratory examinations, the disease must be designated temporarily as "Activity Undetermined." If a provisional estimate of the probable clinical status is necessary for public health purposes, the terms a) "Probably Active", or b) "Probably Inactive" may be used. Every effort should be made to classify cases and to avoid this category.

Exercise Status

The exercise status of a patient at the time of classification shall be designated:

I. The patient not ambulatory
II. The patient has been ambulatory for less than one hour daily.
III. The patient has been ambulatory for one hour daily for a period of two months.
IV. The patient has been ambulatory for at least two hours daily for a period of at least two months.
V. The patient is living under ordinary conditions of life.

The exercise status of a patient shall be designated following the designation of the roentgenologic, symptomatic, and laboratory status; for example, Inactive (6 months) III.

DIFFERENCES IN 1940 AND 1950 EDITIONS

1940 Edition	*1950 Edition*
Clinical Status, p. 21, 1940 Edition, "Diagnostic Standards"	Clinical Classification, 1950 Edition
For the transition period it is necessary to continue these 1940 definitions in current print. The terms defined antedate the 1940 definitions by a number of decades and both the terms and the definitions have been fixed in legislation, regulation, and usage, both lay and professional.	The new terms and definitions are placed opposite the 1940 terms and definitions from which they can be roughly translated.
The 1940 definitions appear below in quotes and no word is changed or deleted, but material that has been significantly revised or deleted in the 1950 edition is here indicated in CAPITALS enclosed in []. Footnotes (1 to 4) are added to help in transposing to the new classification.	The significant additions or changes in the new definitions are *italicized*. The table of "Exercise Status" is a new component of the Clinical Classification and is a necessary addition to each group in order to translate from the old to the new edition.
"[APPARENTLY CURED]."	Roentgenologic, Symptomatic, and Laboratory Status
"[CONSTITUTIONAL] symptoms absent. Sputum, if any, must be found negative for tubercle bacilli, not only by concentration and microscopic examination, but also by culture or animal inoculation. (See page	*Inactive*
	The appearance of lesions by *serial roentgenograms must be stable except for ex-*

26.) In case there is no sputum, the fasting gastric contents should be obtained and similarly examined. Lesions stationary and apparently healed according to x-ray examination.[1] [THESE CONDITIONS SHALL HAVE EXISTED FOR A PERIOD OF TWO YEARS UNDER ORDINARY CONDITIONS OF LIFE.]"

"[A CONSIDERABLE BUT UNDETERMINED PERCENTAGE OF APPARENTLY CURED PATIENTS PARTICULARLY THOSE WHO HAVE FULFILLED THE ABOVE REQUIREMENTS NOT ONLY FOR TWO, BUT FOR SIX YEARS, MAY IN REGARD TO THEIR SURVIVAL EXPECTANCY (AS TO TUBERCULOSIS) REACH NORMAL STANDARDS.]"

"Arrested"

"[CONSTITUTIONAL] symptoms absent. Sputum, if any, must be concentrated and found microscopically negative for tubercle bacilli. (See page 25.) Lesions stationary and apparently healed according to x-ray examination; no evidence of pulmonary cavity.[1] [THESE CONDITIONS SHALL HAVE EXISTED FOR A PERIOD OF SIX MONTHS, DURING THE LAST TWO OF WHICH THE PATIENT HAS BEEN TAKING ONE HOUR'S WALKING EXERCISE TWICE DAILY, OR ITS EQUIVALENT.]"

"[APPARENTLY ARRESTED]"

"[CONSTITUTIONAL] symptoms absent. Sputum, if any, must be concentrated and found microscopically negative for tubercle bacilli. (See page 25.) Lesions stationary and apparently healed according to x-ray examination; no evidence of pulmonary cavity.[1] [THESE CONDITIONS SHALL HAVE EXISTED FOR A PERIOD OF THREE MONTHS, DURING THE LAST TWO OF WHICH THE PATIENT HAS BEEN TAKING ONE HOUR'S WALKING EXERCISE DAILY, OR ITS EQUIVALENT.]"

tremely slow shrinkage and there must be no roentgenologic evidence of cavity. Symptoms of *tuberculous origin* must be absent. Sputum, if any, must be found negative for tubercle bacilli repeatedly, not only by concentration and microscopic examination, but also by culture or animal inoculation.

When a patient is not raising sputum *or when there is any question as to the authenticity or adequacy of expectorated sputum specimens,* the fasting gastric contents *or pulmonary secretions which have been aspirated from the tracheobronchial tree* should be examined by culture or animal inoculation. *These conditions shall have existed at least six months. The period of inactivity shall be designated, if known; for example, Inactive (6 months), Inactive (1 year), Inactive (2 years), et cetera.*

Arrested

The symptomatic and roentgenologic requirements of this group are the same as for "inactive." When sputum specimens or gastric contents have been found negative only by microscopic examination of concentrates and not by culture or animal inoculation, such patients cannot be classified "inactive." They may be classified "arrested" even though culture or animal inoculation may be positive and, *among many concentrated specimens of sputum examined microscopically, an occasional positive may be found.* These conditions shall have existed *at least three months. The period of arrest shall be designated, if known; for example, Arrested (6 months), Arrested (1 year), Arrested (2 years), et cetera.*

1940 Edition

"[QUIESCENT]"

["NO CONSTITUTIONAL SYMPTOMS. SPUTUM, IF ANY, MAY CONTAIN TUBERCLE BACILLI. LESIONS STATIONARY OR RETROGRESSIVE ACCORDING TO X-RAY EXAMINATION; CAVITY MAY BE PRESENT. THESE CONDITIONS TO HAVE EXISTED FOR AT LEAST TWO MONTHS DURING WHICH TIME THE PATIENT HAS BEEN AMBULANT.]"

"[FRANKLY] Active"
Improved
Unimproved
"[SYMPTOMS UNCHANGED, WORSE OR LESS SEVERE BUT NOT COMPLETELY ABATED.][4] Lesions not completely healed or progressive according to x-ray examination. Sputum almost always contains tubercle bacilli."

1950 Edition

Active

Lesions may be stationary, retrogressive, or progressive, according to examination of serial roentgenograms. Symptoms of tuberculous origin may be present or may have been present recently. Sputum *and gastric contents* almost always contain tubercle bacilli, although *in some instances, tubercle bacilli cannot be demonstrated even after repeated cultures and animal inoculations. The period of activity should be designated if known; for example, Active (17 months), Active (3 years).* The designations Active, *Improved,* or Active, *Unimproved,* may be used *after an adequate period of observation or treatment.*

Activity Undetermined

When activity has not been determined from adequate roentgenologic and laboratory examinations, the disease must be designated temporarily as "Activity Undetermined." If a provisional estimate of the probable clinical status is necessary for public health purposes, the terms a) *"Probably Active,"* or b) *"Probably Inactive"* may be used. Every effort should be made to classify cases and to avoid this category.

[1] The wording, but not the sense, of this sentence has been changed.

[2] May now be designated under "Exercise Status" and by the known period of "Inactivity" or "Arrested."

[3] Deleted, not because of any inaccuracy in the statement, but because the statement per se forms no part of a criterion for classification.

[4] Rewording of this sentence in the 1950 classification provides for the inclusion of symptom-free patients in the "Active" group.

Examples of transposition of old terms into new is given below

Equivalent Terms

OLD	NEW
Apparently Cured	Inactive (3 years) V
Arrested	Arrested (6 months) IV
Apparently Arrested	Arrested (3 months) III
Quiescent	Active, *improved* (Exercise shall be indicated).
Active	Active (Exercise shall be indicated)
Improved	*Improved*
Unimproved	*Unimproved*

THE AMERICAN REVIEW OF TUBERCULOSIS ABSTRACTS

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CLINICAL STUDIES, TUBERCULOSIS

Primary Tuberculosis.—The rate of regression in the hilar shadow in primary tuberculosis in 100 children was studied. The associated parenchymal focus is usually so insignificant or so deep seated in the lung that it is not demonstrable at roentgenographic examination. The hilar shadow has been shown to be composed of various anatomic substrata: glandular enlargement with general hyperemia; edema and specific tuberculous foci in the gland; a perihilar nonspecific pneumonic process with hyperemia, edema, atelectases, lymphangitis, and specific tuberculous nodes in the parenchyma of the lung. As long as fever is present as a manifestation of primary tuberculous infection, one may expect an increase of the hilar density. After the initial fever has subsided there is no evident change in the radiologic appearance or size of the hilar enlargement during the ensuing three months and sometimes up to four or five months. This characteristic stability in the hilar density in primary tuberculosis, at least during the first three months, is a basic phenomenon and unquestionably may serve as a basis for comparison in the assessment of hilar densities under other conditions or in affections other than tuberculosis. From this date on there is a progressive decrease in size and increase in density, but the enlargement is still present six months after its manifestation. Gradually there ensues a regression of the roentgenologic changes with a shrinking and a more distinct outline of the hilar density and finally, usually after the lapse of a couple of years, there is calcification of necrotic areas in the pulmonary parenchyma and the glands. It is important to have this exact knowledge of the typical, "normal" course of primary tuberculosis in order to differentiate tuberculosis from other diseases producing enlargement of the hilar shadows and to judge the effect of specific treatment and prophylactic measures, including BCG vaccination, on the rate of regression of hilar tuberculosis.—*Regression of the hilar density in primary tuberculosis, A. Wallgren & C. Wegelius, Acta tuberc. Scandinav., 1949, 23: 220.*—(*K. T. Bird*)

Avian Tuberculosis in a Child.—Avian tuberculosis is a common disease of poultry; and swine tuberculosis due to tubercle bacilli of the avian type occurs in areas where the disease affects chickens. Ulcerative lesions in the intestines of infected chickens discharge enormous numbers of bacilli. Many alleged cases of avian tuberculosis in man have been inadequately studied and described, casting doubt on the diagnosis. Probable avian tuberculosis occurred in a two and a half-year-old girl who lived on a farm and was in close contact with many chickens. At the age of 22 months she fell ill with fever and symptoms suggesting pneumonia. A roentgenogram of the chest revealed massive involvement of the upper lobe of the left lung. Bronchoscopic examination showed no lesions but material swabbed from the bronchoscope contained acid-fast bacillary forms. Gastric contents were cultured for tubercle bacilli. Only one colony grew and its appearance was not typical of human tubercle bacilli. Subsequent gastric cultures were always negative and the child made a rapid recovery. A guinea pig died 39

days after inoculation with bacilli from the single atypical colony. There were small lesions in the spleen and one in the liver as well as a substernal abscess. Cultures from the spleen and liver were similar to the original colony and appeared to be avian tubercle bacilli. The organisms were virulent for rabbits and chickens but not for guinea pigs. Evidently the original guinea pig was unusually susceptible for, as a rule, this species has a high resistance to avian tubercle bacilli. At first the child reacted more strongly to PPD (0.00002 mg.) than to 0.1 cc. of 1:10,000 dilution of avian tuberculin but later this was reversed. A positive reaction to avian tuberculin was obtained in 30 to 50 per cent of the cattle, pigs, and chickens on the child's home farm. The patient had been away from this farm for three weeks before the gastric aspiration was performed, making it unlikely that the avian tubercle bacilli had been ingested a few hours before they were recovered. There were no known cultures of avian tubercle bacilli in the laboratory where the isolation was accomplished.—*Juvenile tuberculous infection, possibly of avian type, W. H. Feldman, D. W. Hutchinson, V. M. Schwarting, & A. G. Karlson, Am. J. Clin. Path., November, 1949, 25: 1183.—(J. S. Woolley)*

Healing of Tuberculous Pulmonary Cavities.—In 3 cases with tuberculous pulmonary cavities, the cavities were induced to heal by lining them with split-thickness skin grafts and pinch grafts.—*Healing of tuberculous pulmonary cavities by means of skin grafts, A. M. Vineberg, Proc. Soc. Exper. Biol. & Med., August, 1949, 71: 578.—(F. B. Seibert)*

Bronchospirometry.—In the Paseka Sanatorium bronchospirometry is performed by the method described by Jacques Arnauld. An obturating sound is inserted into the bronchus under the skiascopic control. After the obturation of one bronchus, the other half of the lung is examined. The patient is connected with an ordinary spirometer and breathes by mouth while his nose is compressed. This method is simple, convenient, and does not damage the tissue. In the lung functions normally there is no change in the respiratory volume and frequency. If the lung is functionally insufficient, the respiratory volume and frequency change when the opposite bronchus is occluded. If the insufficiency is of a high degree, asphyxia appears and the obturation of the opposite bronchus must be discontinued. A high degree of insufficiency on the side to be collapsed suggests thoracoplasty. Pulmonary tuberculosis is not only variable clinically but produces many functional changes. None of these functional changes is characteristic of a specific lesion.—*Successive bronchospirometry in the active pulmonary therapy (Czech), L. Fury, Rozhledy v tuberk., 1949, 9: 62.—(J. Ilavsky)*

Thoracoplasty.—Thoracoplasty was performed on 180 patients between 1945 and 1948. Good results could be obtained only when the patients were observed carefully over a long period before operation. Thus among the patients at the Paseka Sanatorium the postoperative mortality was only one per cent, due to a very exact selection of cases by one group of phthisiologists. Among the patients operated on at the University Hospital in Brno the mortality was a little over 5 per cent, due to less precise selection by different phthisiologists. The best age for the operation is between 25 and 30 years. There is no contraindication to operating on patients over 50 years of age but the risk is greater than in young people. The results in children are not the best because case selection is more difficult. An important part of the examination is the careful measurement of respiration reserve by bronchospirometry. A resection of 3 ribs diminished the vital capacity by 200 to 400 cc. The interval between thoracoplasty stages must not be longer than three to four weeks in order to ensure adequate compression of the lung.—*Thoracoplasy from the surgical viewpoint (Czech), J. Podlaha, Rozhledy v tuberk., 1949, 9: 17.—(J. Ilavsky)*

Tuberculosis and Antihistaminics.—Daily doses of Neo-antergan, 300 mg., and Phener-

gan (RP3277), 25 mg., were given at bedtime for several months to 30 patients with pulmonary tuberculosis. A few patients had slight symptomatic improvement but no definitive roentgenographic changes could be attributed to the use of these antihistaminic agents.—*Tuberculosis and antihistaminics, T. Millner & A. Hurst, Dis. of Chest, December, 1949, 16: 870.*—(*E. A. Rouff*)

Cavernostomy and Tamponade with PAS.—Since March, 1948, cavernostomy and tamponade have been performed on 38 patients, 30 of whom were considered to be hopelessly ill. There were no fatalities; the secretions from all of the cavities became free of tubercle bacilli in an average of 17 days and all remained negative. Bacilli disappeared from the sputum of 28 patients. In the 10 patients with persistently positive sputum, it was possible to carry out further surgical procedures on the same or contralateral side because of the marked symptomatic improvement. Treatment involved three essentials: (*1*) gradual development of the cavernostomy by means of a stoma between the skin and the cavity; (*2*) regular packing of the cavity with gauze soaked in streptomycin or *p*-aminosalicylic acid; (*3*) closure of the draining bronchus by means of diathermy. Improvement was checked regulary through the cavernostomy with a thoracoscope and the stoma was allowed to retract so that the remaining fistula readily closed spontaneously.—*Cavernostomy and tamponade of pulmonary cavities with para-aminosalicylic acid, G. Maurer, Dis. of Chest, December, 1949, 16: 676.*—(*E. A. Rouff*)

Fluid Versus Elevated Diaphragm.—Because of the concave shape of the lung base, pleural fluid can assume a convexity superiorly and mimic the appearance of an elevated diaphragm in the standard posteroanterior roentgenogram. The first procedure in a case of this type is a careful study of consecutive roentgenograms, for in several instances the sudden appearance of an unexplained "elevation of the diaphragm" in a patient whose earlier films showed no such change was clarified by the additional findings. Fluoroscopic examination of the chest, citrocarbonate to outline the stomach, and pneumoperitoneum are suggested as adjuncts in diagnosis. Roentgenograms taken in lateral decubitus are frequently, but not always, diagnostic. The most important feature in the diagnosis of this condition is a high index of suspicion.—*Infrapulmonary pleural effusion simulating elevation of the diaphragm, E. Rothstein & F. B. Landis, Am. J. Med., January, 1950, 8: 46.*—(*T. H. Noehren*)

Planigrams in Tuberculosis.—A review of 300 consecutive sets of planigrams was made to determine the value and limitations of planigram diagnosis in pulmonary tuberculosis. Comparison with surgical specimens and sputum studies was used as a criteria for accuracy. Rigid criteria for diagnosis of a cavity on planigrams were described: (*1*) There must be a complete, sharply defined oval or annular density surrounding an area of increased radiolucence, usually showing on 2 or more roentgenograms at consecutive levels. (*2*) The walls of the suspected cavity must be clearly identified apart from adjacent structures. (*3*) The suspected cavity should correspond in location with the site of the original cavity in cases where collapse therapy has been done. (*4*) In the case of a large radiolucent area within a dense postthoracoplasty lung, identification of a bronchus leading into or stopping just short of the suspicious "highlight" is helpful in diagnosis of cavity. Planigrams are most helpful in dense postthoracoplasty lungs, the extrapleural Lucite pack, the inspissated cavity, and in dense fibrocaseous lesions. They are of limited value in (*1*) confluent nodular densities which are scattered throughout the lung in several planes and which have ulcerations too small to be demonstrated on planigrams, (*2*) the slit-like cavity with collapsed walls in a thoracoplasty lung, and (*3*) emphysematous blebs and bronchiectatic dilatations within a fibrotic upper lobe which may be difficult to distinguish from small tuberculous cavities. In not a single case was a cavity discovered on the plani-

gram in an area where no infiltration was seen in the chest roentgenogram.—*Evaluation of planigrams in pulmonary tuberculosis, P. Morgenstern, C. E. Carr, & W. L. Nalls, Am. J. Roentgenol., September, 1949, 62: 402.—(T. H. Noehren)*

CLINICAL STUDIES, NONTUBERCULOUS DISEASES

Acute Friedländer's Pneumonia.—Roentgenograms of 16 cases of acute Friedländer's pneumonia were reviewed and compared with those of 33 miscellaneous cases of acute pneumonia and 25 cases of pneumococcal pneumonia with bacteremia. The size of the affected lobe, the appearance of the margins of the pneumonia infiltrate, the occurrence of abscess formation, the presence of bronchopneumonia, and the radiopacity of the pneumonic shadow were recorded and comparison was made among the three groups of cases. Bulging of a fissure, sharp advancing borders of the infiltrate, and abscess formation were found to occur in acute Friedländer's pneumonia with considerably greater frequency than in other types of pneumonia. A purely bronchopneumonic form of Friedländer's pneumonia was not encountered in this series. The pneumonic infiltrate in Friedländer's pneumonia was relatively radiopaque but shadows of similar density were commonly found in other types of pneumonia. While the roentgenologic findings in Friedländer's pneumonia are not pathognomonic, in many instances it is possible to suggest the correct diagnosis from the roentgenogram. (Authors' summary.)—*Roentgen findings in acute Friedländer's pneumonia, B. Felson, L. S. Rosenberg, & M. Hamburger, Jr., Radiology, October, 1949, 53: 559.—(W. J. Steininger)*

Chronic Cholesterol Pneumonitis.—In 11 cases of chronic pneumonitis treated surgically, the outstanding feature was the deposition of cholesterol and cholesterol esters in the air spaces. There was no other lung disease. Roentgenographically, this type of pneumonitis was confused with tumor, lung abscess, and infarct. In 5 cases there was rather extensive involvement of a lobe, with a moderate degree of associated collapse. In 6 cases the area of increased density involved only a part of one or more segments of a lobe, the shadow lying against the pleura either peripherally or along a fissure. Hilar and mediastinal lymphadenopathy were sometimes apparent and rarely there were small cavities. Whether this type of chronic pneumonitis is a definite entity is questionable. Some obstruction of the smaller bronchi or bronchioles was often present and may have been a determining factor in the reaction. There is no reason to believe that the end result of the process is abscess formation or bronchiectasis. The evidence at hand favors fibrosis as the final stage.—*Correlation between the roentgenologic and pathologic findings in chronic pneumonitis of the cholesterol type, L. L. Robbins & R. C. Sniffen, Radiology, August, 1949, 53: 187.—(W. J. Steininger)*

Q Fever Pneumonia.—The chest roentgenograms of 77 patients with Q fever admitted to Southern California hospitals were studied. Of these, 65 patients (84 per cent) had pneumonia of varying extent; 13 (24 per cent) of those with pneumonia had bilateral involvement. Spread by direct extension occurred frequently. Migratory lesions were rarely encountered. The most characteristic radiographic lesion (83 per cent) was a homogeneous segmental or lobar consolidation. Increased hilar density, accentuated pulmonary vascular shadows, and hilar or mediastinal adenopathy were notably absent. Minor pleural exudates were seen in almost one-third of the cases. Pneumonic consolidations appeared as early as one day after the onset of symptoms. Resolution usually began with the return of temperature to normal and was completed quickly, but frequently it was delayed. Roentgenologically, Q fever closely resembles pneumococcic pneumonia. It often differs considerably in appearance from the atypical pneumonias.—*Roentgen manifestations of Q fever, G. Jacobson, R. B. Denlinger, & R. A. Carter, Radiology, November, 1949, 5: 739. (W. J. Steininger)*

Miliary Coccidioidomycosis in a Child.—This is the first recorded case of the miliary type of coccidioidomycosis in a child. A seven-year-old Negro girl living in the San Joaquin Valley had a lumbar lesion simulating a Pott's abscess. Ten days prior to being seen she had struck her side and complained of local discomfort since that mild injury. A Mantoux test with tuberculin 1:1,000 was negative, while coccidioidin 1:100 produced a 3 plus reaction. Chest roentgenograms showed widespread miliary lesions which progressed rapidly within a few weeks. Aspiration yielded pus free of acid-fast organisms, and a pure culture of *Coccidioides immitis* was grown from it. Death followed 56 days after the onset of symptoms. —*Miliary coccidioidomycosis of the lungs, report of a case in a child, R. Cohen & R. Burnip, Ann. Western Med. & Surg., December, 1949, 3: 413.*—(*E. A. Rouff*)

Diffuse Interstitial Fibrosis.—Two new cases of diffuse interstitial fibrosis were seen in Uruguay in 1946 and 1948. They were similar to the 4 reported by Hamman and Rich in 1944 and other cases subsequently reported by other authors. The first patient was a 63-year-old white woman with a two-month history of dyspnea, dry cough, and more recent cyanosis. The chest roentgenogram showed a generalized, irregular mottling throughout both lung fields. The clinical course was steadily downhill and the patient expired four months after the onset. At post-mortem examination there were dense, carnified lungs with apparently normal pleurae. Histologically, the interstitial tissue was strikingly thickened by very young, vascular granulation tissue composed predominantly of fibroblasts but containing other cellular elements. This tissue invaded and encroached upon the alveolar spaces. There were also areas of endothelial hyperplasia and metaplasia to the stratified squamous type of epithelium. In the involved areas the elastic fibers were almost completely absent and several areas of bronchiectasis were noted. Some areas of the lung maintained a normal architecture and others showed emphysema. The second patient was a 41-year-old white male with a history of chronic cough for several years. For one year he had noted dyspnea, increased cough, and expectoration of mucopurulent sputum. For a few months dyspnea had been marked and weight loss had occurred. The chest roentgenogram showed multiple, disseminated, nodular shadows in both lung fields, more marked in the basal portions. The course was rapidly downhill with cyanosis and progressive dyspnea. The patient died of respiratory insufficiency two months after admission to the hospital. Only a portion of the right lower lobe was available for post-mortem examination. The changes observed in this were very similar to those of the preceding case. However, the degree of bronchiectasis was much more marked and the arteries showed in some cases considerable reduction of the lumen as a result of intimal proliferation. The main pathologic picture was again a striking interstitial proliferation of young granulation tissue. Both of these cases showed as predominant clinical features dyspnea and cyanosis. The serology was negative. The sputum was negative for tubercle bacilli and fungi. No history of exposure to known toxic agents was obtained. Neither patient showed polycythemia. No clinical evidence of right cardiac failure developed and both patients died of respiratory insufficiency.—*Neumofibrosis intersticial evolutiva. Una neuva entidad? M. Ferrar, N. L. Caubarrere, M. D. Bottinelli, C. Mendilaharsa, & D. Giudice, Hoja tisiol., September, 1949, 9: 207.*—(*F. Perez-Pina*)

Egg Shell Calcifications in Silicosis.—Characteristic calcific densities of unique morphology occur in the chest roentgenograms of men with silicosis. These shadows are circular or ovoid rings in the hilar or mediastinal regions; they consist of an irregular peripheral shell with a faint stippling throughout the enclosed tissue. These "egg shell" or "mulberry" calcifications occur as the result of the silica without any superimposed tuberculous infection and probably without any other infection. They appear long after the original exposure, espe-

cially in milder cases; they are not seen in severe cases terminating in death a few years after exposure. The characteristic calcifications develop in previously affected lymph nodes but not in lung tissue. Calcium deposition begins diffusely throughout the node but later becomes more prominent beneath a heavy capsule that forms around the node. The peculiar configuration of the calcium deposit seems to be characteristic of, and unique to, silicosis but it might occur in chronic, noncaseating lymphadenitis of other origin.—*"Egg shell" calcifications in silicosis, C. E. Grayson & H. Blumenfeld, Radiology, August, 1949, 53: 216.*—(*W. J. Steininger*)

Active Bronchopulmonary Lithiasis.—Seven cases of active bronchopulmonary lithiasis are reported; 6 were proved at surgery; in the seventh the stones were expectorated. This raises to 103 the number of cases reported in the American and English literature since 1900. Active bronchopulmonary lithiasis is supposedly a rare syndrome but probably occurs more often than is suspected clinically. It should be included in the differential diagnosis of every case of bronchial obstruction, pulmonary suppuration, and hemorrhage associated with paroxysmal attacks of cough where the chest roentgenogram shows calcific shadows in the region of consolidated areas. In the majority of cases broncholiths are due to perforation of calcified tuberculous lymph nodes. Laminagraphy is an important diagnostic aid as it may demonstrate the stone perforating the bronchial wall or lying in the lumen. Early recognition and treatment of this condition may prevent the serious complications caused by bronchial obstruction, pulmonary suppuration, and hemorrhage.—*Active bronchopulmonary lithiasis, E. Freedman & J. H. Billings, Radiology, August, 1949, 53: 203.*—(*W. J. Steininger*)

Calcification in Histoplasmosis.—The author previously had surveyed a large group of Kansas City school children. Several hundred were found to have positive histoplasmin skin tests, negative tuberculin reactions, and pulmonary infiltrations by roentgenogram. These children have now been followed for as long as four years. Some of the lesions disappeared, others became fibrotic, but the majority developed calcifications. All the children were asymptomatic throughout the survey. Serial roentgenograms of 17 children whose lesions calcified showed that the precalcific lesions include multiple disseminated lesions of varying sizes which later calcified; hilar node enlargement which progressed to calcification; and pneumonic and nodular lesions which became scattered, small, calcific nodules or larger single homogenous calcified areas. The children remained tuberculin-negative throughout this period of observation.—*Development of calcification in pulmonary lesions associated with sensitivity to histoplasmin, M. L. Furcolow, Pub. Health Rep., November 4, 1949, 64: 1363.*—(*S. Hadley*)

Potential Source of Histoplasmosis.—The source of the infectious agent and the mode of human infection with histoplasma have been sought for but never established. Recently the fungus has been isolated from wild rats in Virginia and Georgia and in skunks. (Pub. Health Rep., 1949, *64:* 1423). However the relationship of the disease in rodents to that in man remains obscure. In this study, 387 samples of soil and debris were collected from farm premises in the environs of Loudon County, Virginia, where the infected rats had been discovered. From 2 of these specimens *Histoplasma capsulatum* was isolated by inoculating mice intraperitoneally. A few macroconidia were observed on direct visualization of the soil also. Although initial isolation was never successful on Saboraud's agar, it is possible to complete the saphrophytic cycle of histoplasma in sterile soil of high humus content. Thus soil may serve as a source of human infection.—*Isolation of Histoplasma capsulatum from the soil, C. W. Emmons, Pub. Health Rep., July 15, 1949, 64: 892.*—(*S. Hadley*)

Hydatid Disease.—Hydatid cysts in the lung frequently are silent. They may cause such pressure effects as atelectasis or bronchi-

ectasis, and are prone to infection with abscess formation. The cyst may involve the pleura and be concealed by the resultant effusion. Hydatid disease is frequently associated with chronic cough and hemoptysis. Occasionally the cyst ruptures into a bronchus with spontaneous resolution. Radiologically, hydatids of the lung may be divided into 5 groups according to their appearance: (*1*) rounded opacities which simulate neoplasms and metastatic deposits; (*2*) ring shadows which may be mistaken for lung abscesses, tuberculous or other cavities, congenital cysts, and interlobular effusions; (*3*) calcified opacities which may be confused with dermoid cysts and tuberculous foci; (*4*) opacities abutting on the pleura which must be distinguished from encysted pleural effusions, pleural neoplasms, and metastases; and (*5*) opacities abutting on the mediastinum and simulating dermoid cysts and mediastinal enlargements. —*Hydatid disease, S. F. Oosthuizen & M. H. Fainsinger, Radiology, August, 1949, 53: 248.*—(*W. J. Steininger*)

Hydatid Disease in Paraguay.—Hydatid disease in humans is practically unknown in Paraguay. Four cases of the pulmonary form of the disease were discovered in 100,000 chest roentgenograms taken between 1941 and 1948. The diagnosis was made on the basis of roentgenographic appearance and a positive Casoni reaction. They were not explored surgically. In 1,800 necropsies not a single case was found. However, in cattle in the period 1944 to 1947, out of 1,292,729 animals slaughtered, 438 cases (0.034 per cent) of echinococcus cysts were found with a ratio of 7 pulmonary to one of the hepatic forms. There is thus an animal reservoir of the disease which constitutes a potential threat as a source for human infections.—*Estado actual de la hidatidosis en el Paraguay, A. R. Gines, Hoja tisiol., September, 1949, 9: 244.*—(*F. Perez-Pina*)

Sternal Marrow in Hodgkin's Disease.—Hodgkin's lymphogranulomatosis is not a disease of the lymph nodes exclusively. Lesions may be widespread, following more closely the distribution of the reticulo-endothelial system than that of any other system. Although the ultimate diagnosis in many cases depends upon the appearance of the affected lymph node, 12 per cent or more of patients with Hodgkin's disease do not show any lymphadenopathy for a long period. Laboratory and clinical observations were made on 35 patients in whom Hodgkin's disease was diagnosed by biopsy or autopsy. Each patient had a complete hematologic examination and a thorough study of aspirated bone marrow. There were 20 males and 15 females, the youngest patient being 10 years of age and the oldest 75 years; 24 were in the age group of 10 to 40 years. Lymphadenopathy was found in 34 patients, the cervical glands being involved in 32, the axillary in 18, and the inguinal in 16. The spleen was palpable in 16 and the liver was enlarged in 13. Roentgenograms of the chest revealed evidence of enlarged hilar glands or lung infiltration in 24 patients. Cutaneous involvement was noted in 3 instances. The blood picture findings were disappointing from a diagnostic standpoint. Definite anemia, usually normocytic, was present in only about one-half of the patients, and in 27 there were more than 3,000,000 erythrocytes per cu. mm. The leukocyte count ranged from 5,000 to 15,000 in more than half the patients, being somewhat below or above this in the remainder. The differential leukocyte pattern was not characteristic; a few patients had an increased percentage of eosinophils and 2 patients had 17 and 27 per cent, respectively. The most constant finding in the bone marrow was myeloid and megakaryocytic hyperplasia. The morphologic pattern of the granulopoietic tissue was that seen in chronic toxic states. The panhyperplasia of the bone marrow simulated that of Banti's disease. A pathologic type of megakaryocytopoiesis involving the lymphoid megakaryocytes was observed in some cases producing atypical platelets. Reed-Sternberg cells were not seen in aspirated sternal marrow nor in histologic sections of bone marrow particles. Evidence is presented to show that giant cells of Hodgkin's granuloma are neither similar to nor related to bone marrow megakaryocytes. The

finding of increased numbers of normal or atypical plasma cells, eosinophils, and reticular cells was neither a constant nor a specific pattern of the bone marrow in Hodgkin's disease. Eosinophilia of the bone marrow could not be correlated with peripheral blood eosinophilia. The accurate diagnosis of the disease was established only by finding the specific pleomorphic lesion of Hodgkin's granuloma. This was best observed in the histologic section of an involved lymph node. The finding of any one cell or a group of cells in sternal aspirated bone marrow smears was insufficient evidence for the diagnosis of Hodgkin's disease.—*Sternal marrow studies in Hodgkin's disease: A review of the literature and a report of thirty-five cases, L. R. Limarzi & J. T. Paul, Am. J. Clin. Path., October, 1949, 19: 929.—(J. S. Woolley)*

Electrocardiograms in Sarcoidosis.—Electrocardiograms from multiple unipolar leads revealed left ventricular hypertrophy in 7 patients with pulmonary manifestations of Boeck's sarcoid. Electrocardiograms of 20 patients with far advanced pulmonary tuberculosis showed various diagnostic changes but in none was there evidence of left ventricular hypertrophy. This finding may prove to be of value in the differentiation of sarcoidosis from tuberculosis.—*Electrocardiographic evaluation of Boeck's sarcoid and advanced pulmonary tuberculosis, S. R. First, Am. J. Med., December, 1949, 7: 760.—(T. H. Noehren)*

Conflagration Pneumonitis.—The Cocoanut Grove disaster took place on November 28, 1942. Among the patients treated at Massachusetts General Hospital, there were 29 with serious involvement of the respiratory tract. In a follow-up study, 16 were examined, questionnaires were answered by mail for 6, and 7 could not be traced. Of the 6 who were checked by mail, 2 are dead and one is psychotic. The remaining 3 added to the group of 16 examined makes a total of 19. Of these, 2 complained of dyspnea, none of cough, and 3 of expectoration. On physical examination, 15 patients had no significant findings and one had a few rales. Roentgenographically, 13 were negative. In 3 there were basal linear streaks; in one, these were present at the end of the original period of observation. It is concluded that there is no permanent pulmonary damage resulting from the thermal injuries.—*Pulmonary effects of the Cocoanut Grove fire, H. S. Pittman & R. Schatzki, New England J. Med., December 22, 1949, 241: 1008.—(A. G. Cohen)*

Pancoast-Tobias Syndrome.—While superior pulmonary sulcus tumors are not rare, only about a hundred case reports have been published. The histologic nature of the tumor varies and the symptoms are characteristic only because of its location. Pressure on the sympathetic nerve fibers and on the brachial plexus causes the early symptoms; pulmonary symptoms are late, rarely dominating the clinical picture. A portion of the tumor may be in the thorax and play no part in the production of the typical syndrome. The mass that causes the symptoms lies behind the pleural dome in the retropleural sulcus of Sébileau at the emergence of the roots of the seventh cervical to the third dorsal spinal nerves. The tumor usually is a bronchogenic carcinoma, but may be a sarcoma, Hodgkin's disease, tuberculosis, or bronchial neoplasm. The tumor mass may be primary or metastatic. The earliest symptom is paroxysmal pain, first in the shoulder and then usually along the inner border of the arm. Heat, cold, and tactile sensations become altered; loss of strength in the fingers and hands occurs, with wasting of the thenar, hypothenar, and interosseous muscles. Reflexes usually remain normal. Involvement of the cervical sympathetic nerve fibers, as evidenced by the Claude Bernard-Horner syndrome, rarely is lacking. Four additional cases are reported. Three patients had typical symptoms; one had hemoptysis and no pain.—*Le Syndrome de Pancoast et Tobias, J. Chenebault, Le Poumon, July–August, 1949, 5: 269.—(A. T. Laird)*

Carcinoma from Paraffinomas.—Highly refined vegetable oils such as those commonly

used in iodized oils are free of fatty acids and do not produce evidence of inflammatory reaction when injected into the lung. Ultimately they are eliminated without evident damage to the lung. When spoiled or rancid, however, vegetable oils may become irritating and should not be injected. Animal oils have a high content of free fatty acid, are extremely irritating, and produce lipoid pneumonia which may be fatal. If recovery occurs the oily particles may be completely eliminated. Mineral oil also produces damage when introduced into the lung because the oil cannot be saponified or digested by the phagocytes, and oily droplets remain in the tissue. An accumulation of such droplets surrounded by dense walls of fibrous tissue constitutes a paraffinoma. Paraffinoma may cause pressure on the larger bronchi with partial obstruction and bronchiectatic dilatation. They may produce local inflammation and erosion or they may be the basis for the development of bronchiogenic carcinoma. Carcinomatous tissue may appear grossly so similar to paraffinoma that association of the two conditions is overlooked unless many areas of the tumor mass are examined. Two cases of bronchiogenic carcinoma are reported, one of which undoubtedly was in a pre-existing paraffinoma. The other was associated with lipoid pneumonia.—*The fate of oil particles in the lung and their possible relationship to the development of bronchiogenic carcinoma, L. R. Sante, Am. J. Roentgenol., December, 1949, 62: 788.—(T. H. Noehren)*

Pseudo-adenomatous Basal-cell Metastases.—Five cases of pseudo-adenomatous basal-cell carcinoma (mucous and salivary gland tumor) with metastasis to the lung are reported. The evidence presented suggests that this neoplasm metastasizes relatively frequently. The growth rate of the pulmonary metastases, like that of the primary tumor, is slow and the patient may be asymptomatic for years. Unless chest roentgenograms are made, the pulmonary lesions will be overlooked. Unlike most malignant tumors, the development of pulmonary metastases of this neoplasm does not necessarily presage an early fatal outcome. (Authors' summary)—*Pulmonary metastases of pseudo-adenomatous basal-cell carcinoma (mucous and salivary gland tumor), I. Lampe & H. Zatzkin, Radiology, September, 1949, 53: 379.—(W. J. Steininger)*

Bronchiectasis.—A significant percentage of the patients afflicted with permanent dilatation of the bronchi gave a past history of measles, pertussis, and pneumonia. Contact with individuals who cough was not statistically significant. The most common symptom of bronchiectasis was cough, usually productive. There was little correlation between the extent of the bronchographic changes and the quantity of sputum. Hemoptysis was present in 19 cases. Dyspnea, pain in the chest, and loss of weight were variable and depended upon the degree of involvement. Clubbing was noted in 6 patients. Abnormal physical signs were variable. In the plain roentgenograms, diagnostic features were present in 34 per cent: (*1*) thin-walled ring shadows 3 to 15 mm. in diameter, (*2*) recurring ill-defined woolly shadows at the bases, (*3*) change in normal contour of the pulmonary artery shadow, (*4*) basal striations extending below the dome of the diaphragm, and (*5*) in the left lower lobe, a straight heart border. Bronchographically, dilatations were fusiform in 25, saccular in 3, and mixed in 7. The life expectancy was less gloomy than previously suspected.—*A clinical survey of bronchiectasis, B. Mann, Tubercle, November, 1949, 130: 254.—(A. G. Cohen)*

Anomalous Pulmonary Artery.—Three cases of anomalous pulmonary artery are described. All of them were studied post mortem. In the first case there was a lower accessory pulmonary artery starting from the abdominal aorta. In the second case a similar artery was found originating from the thoracic part of the descending aorta. The bronchial tree was normally developed. In the third case the left branch of the pulmonary artery was absent and the lung was supplied by an upper accessory artery originating from the descending part of the aorta.—*Accessory pulmonary artery*

(*Czech*), *H. Sikl, Rozhledy v tuberk., 1949,* **9:** *211.*—(*J. Ilavsky*)

Aneurysm of Phrenic Vessels.—A 39-year-old woman gave a history of pleural effusion at the age of 15, for which several thoracenteses were performed. Two years later, in the course of a physical examination, a continuous bruit was heard over the ninth intercostal space in the posterior scapular line, the area in which the thoracenteses had been done. Roentgenograms of the chest showed small areas of calcification suggestive of phleboliths in the same region. Because of pain in the lower part of the chest and in the region of the right shoulder the patient was operated upon. An arteriovenous fistula of the right phrenic vessels was successfully excised. Following the operation the patient was asymptomatic and the bruit could not be heard.—*Arteriovenous aneurysm of the phrenic vessels: Report of a case following thoracentesis, D. C. Elkin, J.A.M.A., October 22, 1949,* **141:** *531.*—(*H. Abeles*)

Arteriovenous Fistula.—Pulmonary arteriovenous fistula is being reported with increasing frequency. Forty-three cases have been collected and 2 new ones added. The lesion is often part of the hereditary hemorrhagic teleangiectasia of Rendu-Osler-Weber's syndrome. The manifestations are cyanosis, clubbing, dyspnea, polycythemia, bruit, and a typical pulmonary shadow. The main complications are pulmonary hemorrhage from rupture of the vessels and polycythemia with thrombosis, especially of cerebral vessels. The treatment is surgical. If the fistulas, which are often multiple, do not occur in too many lobes this is curative. (Authors' summary).—*Pulmonary arteriovenous fistula (varix): Review of the literature and report of two cases, W. M. Yater, J. Finnegan, & H. M. Giffin, J.A.M.A., October 29, 1949,* **141:** *581.*—(*H. Abeles*)

Cavernous Pulmonary Telangiectasis.—Cavernous pulmonary telangiectasis is characterized by a wide peripheral communication between a dilated, tortuous, thin-walled pulmonary artery and the corresponding vein. It is but one manifestation, often the most conspicuous, of the disease known as generalized telangiectasis. A typical case was treated by excision of the lingula. The bronchi of the resected specimen were immediately injected with formalin and the large vessels and sac were distended with gelatin. The specimen was allowed to harden and later was dissected. The dilated branch of the pulmonary artery to the lower segment of the lingula entered a large peripheral sac. This, in turn, was drained by two lingular veins which were not unusually long or wide. The sac thus occupied the usual position of pulmonary capillaries. There were many small dilated vessels in the position of pulmonary arterioles scattered throughout all segments of the specimen. These telangiectases are comparable to those found in the skin and mucous membranes. Objection is raised to the term arteriovenous fistula; this should be reserved for artificial communications. In telangiectasis the blood by-passes the normal capillaries and is not oxygenated; a compensatory polycythemia results. When the lesion is excised, the normal red blood count is restored by increased blood destruction. The cardiac output generally is normal as there is sufficient compensation. There is often a family history of telangiectasis and the lesions are to be found on the skin and mucous membranes. A history of epistaxis is common. There is evidence to indicate that the condition is humoral in origin and very likely hormonal. Radiographically, a characteristic finding is the increase in the size of the lesion during respiration and decrease during expiration. The only suitable treatment is surgical excision, which should be reserved for cases in which there is a considerable degree of anoxia.—*Cavernous pulmonary telangiectasis, J. Hayward & L. Reid, Thorax, September, 1949,* **4:** *137.*—(*A. G. Cohen*)

Spontaneous Pneumothorax.—This report is based on 97 consecutive cases of simple spontaneous pneumothorax admitted to a general medical center. Eight cases in which the spontaneous pneumothorax complicated a cur-

rent intrathoracic disease process were excluded. Among the 97 patients, the average age was 30.2 years, and the great majority were males. The right hemithorax was involved in 47 cases, the left in 44 cases, and 6 cases were bilateral. Forty-six patients developed slight to moderate pleural effusion; massive hemothorax developed in 3 patients requiring thoracentesis. The average time required for complete re-expansion was four weeks, the shortest was six days, and the longest twelve weeks. Sixteen patients had one recurrence; 8 had two or more. The average time between attacks was 23.2 months. Fifteen patients had recurrences in one year or less and 5 in five or more years after the initial pneumothorax. There were 2 deaths, one from tension pneumothorax, the other from massive hemothorax. The presence or absence of tuberculosis is the diagnostic problem. If tuberculosis is not present at the time of the spontaneous pneumothorax, it is no more likely to develop than in the average individual in a community.—*Spontaneous pneumothorax: A study of 105 cases, L. A. Rottenberg & R. Golden, Radiology, August, 1949, 53: 157.*—(*W. J. Steininger*)

ANTIMICROBIAL THERAPY

Miliary and Meningeal Tuberculosis.—Of 1,212 adult men treated for tuberculosis from January, 1947 to April, 1949, 30 were either admitted for, or subsequently developed, the miliary or meningeal form of the disease. There were 9 cases of miliary tuberculosis, 14 of tuberculous meningitis, and 7 of tuberculous meningitis superimposed on miliary tuberculosis. The miliary group received 1 Gm. of streptomycin intramuscularly with 4 Gm. of Promin intravenously daily for 120 days. The meningitis patients received 2 Gm. of streptomycin intramuscularly with 4 Gm. of Promin intravenously daily and streptomycin 50 mg., intraspinally three times a week for 120 days. The mixed group received streptomycin, 4 Gm., daily for the first two weeks and then 3 Gm. daily up to 120 days with Promin, 4 Gm., daily. There were 3 deaths in the miliary group on the seventh, tenth, and thirty-seventh day of therapy. The remaining 6 patients were living 111 to 534 days after starting treatment; 5 have shown marked or complete clearing and one has moderate clearing. Of the 14 meningitis patients, 11 died and 3 survived to the date of this report. In the mixed group, meningitis was diagnosed on the eighteenth to eightieth day of therapy for miliary tuberculosis in 6 patients. The seventh patient was treated for tuberculous laryngitis for 59 days before meningitis was recognized. Six patients died and one survived to the time of this report, but all showed marked or complete clearing of the miliary lesions. It is remarkable that there was (*1*) no recurrence of pulmonary seeding in any of the miliary cases; (*2*) no pulmonary seeding in any of the patients who developed meningitis first, (*3*) no deaths from uncomplicated miliary tuberculosis patients who survived 6 weeks after the start of therapy; (*4*) no meningitis among patients with miliary disease unless symptoms of meningitis were present during the first two months of therapy; and (*5*) clearing of the miliary lesions in all patients of the mixed group who survived 42 days of therapy even though the meningitis proved fatal in all but one. It would seem that streptomycin in doses of 1 Gm. daily is effective treatment for miliary tuberculosis. In tuberculous meningitis, it would seem futile to expect better results than heretofore with larger doses of streptomycin. Efforts should be aimed primarily at finding some means of bringing the drug into contact with the organisms within the cerebrospinal system. Experiments with trypan blue, iodides, and streptokinase are steps in that direction.—*Streptomycin in the treatment of miliary and meningeal tuberculosis, based on a study of 30 cases, A. Shamaskin, E. J. Des Autels, H. C. Sweany, L. C. Morris, J. R. Zvetna, & J. Mindlin, Dis. of Chest, December, 1949, 16: 765.*—(*E. A. Rouff*)

Fate of Streptomycin.—A mathematical expression for the clearance of streptomycin from the blood was established by experimental data using simultaneous thiosulfate clearances as a measure of glomerular filtration rates.

Streptomycin was found to be excreted unchanged in the urine; its clearance was about 70 per cent of the corresponding glomerular filtration in man as well as in dogs. Since tubular reabsorption did not account for the other 30 per cent, evidence of protein binding was sought. It was found that 30 per cent of the streptomycin was bound to protein and that 50 per cent of this was bound to albumen; the rest apparently being bound to globulins.—*Streptomycin clearance and binding to protein, G. E. Boxer, V. C. Jelinek, & A. O. Edison, J. Pharmacol. & Exper. Therap., September, 1949, 97: 93.*—(*S. Hadley*)

Fate of Streptomycin in the Colon.—Because of the reported favorable effect of streptomycin therapy for intestinal tuberculosis, experiments were conducted to ascertain the fate of rectally instilled streptomycin. Eighteen patients with pulmonary tuberculosis but without intestinal involvement received streptomycin sulfate, streptomycin calcium chloride, and dihydrostreptomycin. Similar results were obtained with each of these drugs, namely, that after rectal instillation of 1 Gm. of streptomycin in 500 cc. of water no drug could be demonstrated in the serum or plasma within the ensuing six hours. Over a corresponding time the urine showed a maximum of 8.87 per cent of streptomycin and 5 had none in the urine. Seven hours after the original instillation of the drug, the colonic contents contained between 6.4 and 62.2 per cent of streptomycin. All patients were subjected to intramuscular streptomycin injection of 0.5 Gm. one week later with the usual curve of the streptomycin blood level. In an *in vitro* experiment streptomycin was added to fresh stool specimens. It was demonstrated that streptomycin disappears from the test tube at a rapid rate. After six hours a loss of 74 per cent of drug was demonstrated.—*Reber Resorption und Allau von Streptomycin im Colon, M. Roost-Pauli & H. Roost-Pauli, Schweiz. med. Wchnschr., October 1, 1949, 70: 942.*—(*H. Marcus*)

Tuberculous Abscess.—A 27-year-old white man was first seen in April, 1940, with a slow-growing tumor on the left side of his chest. A firm tumor was found in the fourth interspace just to the left of the costal margin; the chest was roentgenologically normal. At operation, a cystic tumor was removed and the resulting cavity was drained. The histologic diagnosis was tuberculosis. A sinus tract formed in the chest wall and was excised in January, 1942. During the next five years the tract reopened several times, and in January, 1947, a swelling appeared just above the sinus opening. Yellowish pus was aspirated from the swelling and 1 Gm. of streptomycin dissolved in 2 cc. of isotonic sodium chloride solution was injected on 5 occasions. The swelling disappeared leaving only a tiny indurated area. In the meantime, the sinus tract had opened again. After 22 infiltrations with 1 Gm. of streptomycin around the tract it healed completely. Streptomycin was not administered by any other route.—*Tuberculous abscess successfully treated by aspiration and injection of streptomycin, A. R. Koontz, J.A.M.A., October 15, 1949, 141: 459.*—(*H. Abeles*)

PAS Therapy in Sweden.—Since March, 1944, 378 cases of pulmonary tuberculosis have been treated with *p*-aminosalicylic acid (PAS). In 205 of these, the following criteria were met: (*1*) tubercle bacilli were demonstrated in the sputum by concentration, culture, or guinea pig tests just before treatment; (*2*) the pulmonary process was progressive or stationary for some months without signs of regression; (*3*) moderately or far advanced disease was present with or without complications; (*4*) observation was possible before treatment for at least two months spent at bed rest; (*5*) any collapse therapy was concluded three months before PAS treatment or was instituted three months before treatment, the lesions still showing progression; (*6*) the patient was between 15 and 60 years of age; (*7*) PAS was given orally in an average dose of 14 Gm. daily for at least one month; (*8*) at least three months' observation was possible after PAS therapy. These cases were compared with 223 cases who had received streptomycin, 1.8 Gm. daily, for four months. In approximately 80 per cent of the streptomycin cases, drug-re-

sistant bacilli appeared during treatment. Bacillary resistance to PAS was less pronounced and appeared only after about five months' treatment. Clinically, PAS seemed to produce more marked improvement than streptomycin; roentgenographic improvement was more marked with streptomycin. Bacilli disappeared from the sputum in about the same percentage of patients (43 per cent) treated with either drug, but the diminution in sputum volume was more marked with streptomycin. The lack of toxemic reactions to PAS was a great advantage and allowed early and mild infections to be treated. PAS produced a favorable response in tracheobronchial disease, dramatic improvement in intestinal tuberculosis, and an unfavorable response in encephalomeningeal disease. Miliary tuberculosis responded better to combined streptomycin and PAS than to either alone. In genitourinary disease symptomatic response to PAS alone was excellent, and local PAS therapy in skin tuberculosis was quite encouraging.—*The treatment of tuberculosis in Sweden with para-aminosalicylic acid: A review, J. Lehmann, Dis. of Chest, December, 1949, 16: 684.*—(*E. A. Rouff*)

PAS Resistance.—Most reports on the *in vitro* sensitivity to *p*-aminosalicylic acid (PAS) indicate that human tubercle bacilli are sensitive to low concentrations of the agent. A total of 107 cultures of human tubercle bacilli and 2 cultures of bovine tubercle bacilli have been examined; all, including 15 human-type cultures which were resistant to streptomycin, were sensitive to low concentrations of PAS. Tubercle bacilli from 8 cases treated with PAS alone for prolonged periods were examined; strains from 4 of these were resistant *in vitro* to high concentrations of PAS. No conclusion could be drawn as to the relationship between the sensitivity of the bacilli and the reponse of the patient to therapy. Of a group of 10 patients treated with streptomycin, PAS, and Promin, only one was found after treatment to have streptomycin-resistant bacilli and one other had PAS-resistant tubercle bacilli.—*The occurrence of tubercle bacilli resistant to p-aminosalicylic acid (PAS), A. G. Karlson, A. Delaude, D. T. Carr, K. H. Pfeutze, & W. H. Feldman, Dis. of Chest, December, 1949, 16: 667.*—(*E. A. Rouff*)

Sulphetrone for Pulmonary Tuberculosis.—In 25 patients treated with sulphetrone in 1943, the lesions were predominantly infiltrating. In a few cases, previous collapse measures had been unsuccessful. The dosage was 0.5 Gm. given cautiously every eight hours for a few days; it was then rapidly increased until 6 to 8 Gm. a day were given. The red blood cell count, hemoglobin, and blood sulphetrone level were checked every week. Fluids were restricted to 2 to 3 pints daily. Iron was given to combat the inevitable anemia. Minor toxic symptoms were headache, nausea, and diarrhea, which were never severe. Most patients developed a dusky cyanosis. Clinically, there was some improvement. The sedimentation rate fell, weight increased, and occasionally tubercle bacilli disappeared from the sputum. The results when judged six years later were not very good. Nine patients were dead; 14 of the others required some form of collapse therapy. The other 2 were well and had negative sputum. There was progression in at least 7 cases; in 3 during therapy and in 4 within four years.—*Sulphetrone in pulmonary tuberculosis, H. V. Morlock & R. Livingstone, Lancet, December 24, 1949, 2: 1170.*—(*A. G. Cohen*)

Antibiotics against M. Tuberculosis.—A streptothricin-like antibiotic, termed EI_8, has been isolated from an unidentified *Streptomyces sp.* It is bacteriostatic for *Mycobacterium tuberculosis* H37Rv in dilution of 1:100,000. It closely resembles actinorubin (Kelner, A., and Morton, H. E., J. Bact., 1947, *53:* 695) in its antibacterial spectrum, general properties, and toxicity. However, the 2 organisms *Streptomyces sp.*, EI_8 and A-105, which produce these 2 antibodies are morphologically distinct.—*Search for antibiotics active against mycobacterium tuberculosis. I. A streptothricin-like antibiotic form of streptomyces sp., R. S. Weiser, G. M. Gardner, J. S. Lefler, & L. St. Vincent, Proc. Soc. Exper. Biol. & Med., November, 1949, 72: 83.*—(*F. B. Seibert*)

New Tuberculocidal Compounds.—A total of 28 diphenlymethane derivatives were tested for antibacterial activity against tubercle bacilli. Studies were made in Proskauer—Beck broth and white mice (CFW) were used to evaluate toxicity. Bis (2 hydroxy-5-bromophenyl) methane completely inhibited the growth of tubercle bacilli at 0.25 mg. per 100 cc. This compound has an LD_{50} for mice of 2.0 mg. per Kg. as tested by administration of a single dose. Although di- and tri-chloro derivatives were more active, they were also more toxic.—*Tuberculocidal activity and toxicity of some diphenylmethane derivative, H. J. Florestano, J. Pharmacol. & Exper. Therap., July, 1949, 96: 238.—(S. Hadley)*

Aureomycin in Treatment of Experimental Tuberculosis.—Aureomycin given parenterally in doses approximately 10 times the maximum used for other infections in man failed to influence favorably the course of guinea pig tuberculosis, and exhibited definite toxicity. These results confirmed the findings of Steenken and Wolinsky.—*Failure of aureomycin in the treatment of experimental tuberculosis, T. L. Perry, Proc. Soc. Exper. Biol. & Med., October, 1949, 72: 45.—(F. B. Seibert)*

Aureomycin for Atypical Pneumonia.—Aureomycin produced a prompt and marked beneficial effect on the fever and symptoms in each of 40 patients with the characteristic findings of so-called viral or primary atypical pneumonia. Cold agglutinins were demonstrated in the serum of 32 of these patients in significant or in rising titer at or after the middle of the second week of the disease. The great majority of the patients had a significant drop in temperature within 24 hours after the first dose of aureomycin and were essentially afebrile and symptomatically improved by the end of the second day. There was no definite evidence of extension of the lesion in the lungs after the initiation of aureomycin therapy. In at least 2 patients, however, the day after treatment was started rales first became evident over areas where they had not been heard previously. Complete clearing, as demonstrated by physical signs and roentgenology, occurred in less than ten days in 19 patients, whereas in 4 others infiltrations were still demonstrable more than ten days after aureomycin was begun. The untoward reactions from the oral doses of aureomycin were limited to gastrointestinal symptoms. Recommended dosage schedules are 1.0 Gm. every four to six hours or 0.5 Gm. every three or four hours. In a group of 9 additional patients in whom cold agglutinins were demonstrated but in whom the pulmonary findings were accounted for on the basis of diseases other than primary atypical pneumonia, the response to aureomycin was variable.—*Treatment of primary atypical pneumonia with aureomycin, H. S. Collins, E. B. Wells, T. M. Gocke, & M. Finland, Am. J. Med., January, 1950, 8: 4.—(T. H. Noehren)*

Chemotherapy of Neoplastic Disease.—There is a growing realization that neoplastic tissues are, on the whole, significantly different from normal tissues. This enables one to postulate chemicals that may injure and destroy the former without seriously harming the latter. The available chemicals showing some effect on neoplastic tissues fall into 4 general classes: (*1*) those attacking some physiologically normal function still retained by the cancer cell, illustrated by iodine deposition by thyroid carcinoma; (*2*) those altering the biochemical substrate of the tumor, which still retains relative dependence on such environment, as the estrogens and androgens in mammary carcinoma; (*3*) the great group of bone marrow-lymphoid tissue-destructive or inhibiting agents, which also influence tumors derived from such tissues, including urethane, arsenic, benzene, and the amine mustards; (*4*) the agents which injure the vascular supply of the tumors such as the *B. prodigiosus* polysaccharide. Further clarification of the mode of action of these compounds is important, and may well produce clues to more effective agents of the same general classes. The results of chemotherapy of cancer to date are on the whole disappointing. That progress

is being made is also impossible to deny.—*Experimental chemotherapy of neoplastic diseases, M. B. Shimkin & H. R. Bierman, Radiology, October, 1949, 53: 518—(W. J. Steininger)*

LABORATORY STUDIES

Diagnosis by Bronchial Lavage.—Bronchial lavage was performed once, and in a few instances twice, in 382 individuals; all had previously had repeated examinations of the sputum and gastric lavages which failed to demonstrate tubercle bacilli. The lavage consisted of the instillation of 20 cc. of warm physiologic saline solution through the glottis into the trachea and bronchi, after preliminary anesthetization of the pharynx and tracheobronchial tree with a spray of one per cent pontocaine solution. After allowing two or three minutes for the mobilization of the bronchial secretions by the saline, the patients was encouraged to cough and expectorate into a sterile container. The cases were divided into 3 groups, according to the diagnostic aim of the procedure: (*1*) To establish etiology. In a group of 99 patients suspected of being tuberculous, there were 57 with lesions of the exudative type, 13 with productive lesions, and 29 with mixed type. Of these, 55 were minimal, 35 were moderately advanced, and 9 were far advanced. Tubercle bacilli were demonstrated by bronchial lavage in 24 of these cases (24.2 per cent). Many more positive results were obtained in the exudative and mixed types than in the productive form. (*2*) To determine the activity of known lesions. In this group were 208 patients whose tuberculous lesions had been treated by collapse therapy for six to thirty months and were classified as cured or arrested on the basis of roentgenographic, clinical, and laboratory data. Of these, 127 had intrapleural pneumothorax, 56 had extrapleural pneumothorax, and 12 had phrenic paralysis with pneumoperitoneum; 149 had unilateral collapse and 59, bilateral collapse. In the entire group, 31 patients (14.9 per cent) had tubercle bacilli demonstrated by bronchial lavage. After thoracoplasty, 8 per cent of the patients were positive; with intrapleural pneumothorax, 12 per cent; with extrapleural pneumothorax, 17 per cent; and with phrenic paralysis and pneumoperitoneum, 67 per cent. (*3*) To include tuberculosis as a diagnosis. The remaining 75 individuals had no parenchymatous tuberculous lesions or had lesions attributed to nontuberculous causes. These were divided into 3 subgroups: (*1*) 19 patients with pleuritis without parenchymatous lesions, in all of whom bronchial lavage was negative; (*2*) 33 patients with bronchiectasis, simple silicosis, chronic passive congestion, pulmonary abscess, and pulmonary arteriolitis, all of whom were negative except one previously diagnosed as having simple silicosis; and (*3*) 23 individuals who were clinically, radiologically, and bacteriologically negative. Two of these patients were positive by bronchial lavage. Subsequently laryngo-bronchoscopy revealed discrete laryngeal lesions in one and tracheobronchial disease in the other. In a separate group of 108 patients, bronchial lavage was performed only once, with negative results. Of these, 32 had lesions suspected of being tuberculous and 76 were undergoing collapse therapy. In each of these 108 cases, 2 to 4 gastric lavages and an equal number of sputum examinations were made. In the group with suspicious lesions, gastric lavage was positive in one of 32, and sputum examination was positive in one of 21. Among patients on collapse therapy, one of 76 was positive on gastric lavage, and one of 31 was positive on sputum examination. The results of this study indicate that bronchial lavage is a more efficient diagnostic aid than sputum examination or gastric lavage. Examination of the sputum, however, is still the procedure of choice because of its simplicity and lack of inconvenience for the patient. Bronchial lavage is considered preferable to gastric lavage as regards simplicity, reliability, and slight discomfort to the patient. Three instances of relatively minor side reactions occurred and were attributed to an excessive amount of anesthetic. No more than 4 cc. of a one per cent solution of pontocaine should be used.—

El lavado bronquial en el diagnostico de la tuberculosis pulmonar, E. Staines, Rev. mex. de tuberc., July-August, 1948, 9: 125.—(F. Perez-Pina)

Tuberculin Hypersensitivity Transferred in Man.—Cutaneous tuberculin hypersensitivity was passively transferred in 12 consecutive instances to tuberculin-negative human recipients by means of an intradermal injection of viable leukocytes obtained from the blood of tuberculin-positive human donors. The degree of hypersensitivity induced bore a relationship to the dosage of leukocytes used and the degree of tuberculin hypersensitivity of the leukocyte donor. It was a transient phenomenon which could be repeated. Leukocytes from tuberculin-negative donors were not effective.—*The cellular transfer of cutaneous hypersensitivity to tuberculin in man, H. S. Lawrence, Proc. Soc. Exper. Biol. & Med., August, 1949, 71: 516.—(F. B. Seibert)*

Hyaluronidase in Tuberculosis.—The extension of an experimentally induced tuberculous infection in the skin of rabbits or guinea pigs was increased by the simultaneous injection of hyaluronidase-producing bacteria (*Staphylococci* or *Streptococci*). There was a direct correlation between the enhancing effect of the accompanying bacteria and their capacity for producing hyaluronidase. In many of the experiments the spreading effect was, partly at least, due to enzyme preformed in the bacterial culture. However, other experiments clearly showed that spreading of the tuberculous inflammation may be entirely due to hyaluronidase produced at the site of infection. The generalized tuberculous infection developing in guinea pigs simultaneously inoculated into the skin with tubercle bacilli and hyaluronidase-producing *Staphylococci*, was aggravated and accelerated proportionally to the enzyme production of the strain used. (Authors' summary)—*The effect of bacterial spreading factors on local and generalized experimental tuberculous infection, S. Bergqvist & T. Packalén, Acta tuberc. Scandinav., 1949, 23: 250.—(K. T. Bird)*

Amidase of Tuberculous Tissue.—Homogenates of caseous tuberculous material produced in the lungs and kidneys of rabbits by intratracheal infection with virulent tubercle bacilli can hydrolyze benzoylarginineamide (BAA) at pH 5.1. Hydrolysis proceeds at a more rapid rate than that produced by homologous normal tissues. Greater enzymatic activity was found in the lungs and kidneys of animals first immunized with a nonvirulent culture before reinfection than in those with a primary infection.—*Enzymatic hydrolysis of benzoylarginineamide by normal and tuberculous tissue of rabbits, C. Weiss & J. Schultz, Proc. Soc. Exper. Biol. & Med., October, 1949, 72: 236.—(F. B. Seibert)*

Complement in Tuberculin Cytolysis.—Complement was found to be essential for the *in vitro* cytolysis of human white blood cells by tuberculin. Complement was removed from tuberculous plasma by means of 2 antigen-antibody systems at the zone of equivalence; either with type III polysaccharide and anti-pneumococcal type III rabbit antiserum, or with crystalline bovine albumin and anti-bovine albumin rabbit serum. In the presence of such "decomplemented" tuberculous serum Old Tuberculin did not cause cytolysis of washed white cells. If active complement in the form of freshly drawn type tuberculin-negative serum were added, cytolysis took place. Control experiments, using normal plasma, showed no white cell destruction.—*The role of complement in the lysis of leucocytes by tuberculoprotein, J. M. Miller, J. H. Vaughan, & C. B. Favour. Proc. Soc. Exper. Biol. & Med., August, 1949, 71: 592.—(F. B. Seibert)*

Virulence of Tubercle Bacilli.—Comparison was made between the virulence of tubercle bacilli from European and Mussulman patients in the city of Algiers where tuberculosis morbidity and mortality is considerably higher in the latter group. The cases were divided into acute, subacute, and chronic groups. Equal amounts of a pure culture of tubercle bacilli derived from sputum of each patient was

injected into guinea pigs and the virulence was estimated by the survival time of the animals. A certain correlation could be established between the acuteness and gravity of the disease and the virulence of the organisms. No difference was found in the survival time of guinea pigs injected with cultures from European and Mussulman patients with corresponding types of disease.—*Recherches sur la virulence comparée du B. de Koch chez les tuberculeux pulmonaires Algériens, Européens et Mussulmans, A. Lévi-Valensi, S. Cviklinsky, & M. Vaugier, Rev. de la tuberc., 1949, 13: 448.—(V. Leites)*

Bronchial Dynamism.—The caliber of the bronchus is increased during inspection and reduced during expiration. Regional modifications take place simultaneously at the roots of the bronchial branches, where smooth muscle fibers play the role of functional sphincters. These regional contractions are scarcely noticeable under normal conditions but are very manifest in the presence of irritation of the mucous membrane. The variations of caliber and movement are of great importance in regulating the ventilation of the lungs. Contraction at the root of the bronchus constitutes a retrograde obstacle to the ventilation of affected segments with consequent retention of the secretions. Functional and anatomical changes may follow and mask the simple initial cause. During the act of coughing substantial changes take place in the form and size of the trachea and bronchi, chiefly of their primary and secondary branches. The bronchographic studies presented show that the act of coughing consists of a swift peristaltic wave which runs from the small bronchi toward the trachea. Thoracic and diaphragmatic pressure are secondary factors favoring but not causing expulsion of the bronchial contents. The act of coughing can be accomplished exclusively in a single lung or even in a single lobe. In bronchiectasis the secretions are not expelled by coughing; the mucous and muscular sheets have been destroyed so that the peristaltic wave cannot originate in the bronchiectatic branches. These dynamic characteristics make possible a differentiation between reversible bronchiectasis susceptible to medical treatment, and irreversible bronchiectasis which must be submitted to early surgical treatment.—*Bronchial dynamism, S. DiRienzo, Radiology, August, 1949, 53: 168.—(W. J. Steininger)*

Coagulation in Hemopneumothorax.—A case of hemopneumothorax with recovery is reported, together with observations on the pleural and venous blood coagulation mechanisms. Blood removed from the chest of this patient failed to clot. The thoracentesis specimens were comparable in hemoglobin content, hematocrit, and plasma specific gravity to the circulating intravascular blood. The "incoagulability" of this hemothorax fluid was confirmed on several occasions. The essential constituents for coagulation of blood, i.e., prothrombin, thrombin, and fibrinogen, were determined to be completely absent from the pleural blood specimens. Calcium deficiency was not the basis for the absence of clotting inasmuch as calcium was present in relatively normal and adequate amounts. Furthermore, the hemothorax plasma also failed to clot when recalcified during the performance of the prothrombin determination. It was not possible to demonstrate any form of anticoagulant activity in the pleural blood. The absence of the essential factors for coagulation in the pleural blood of this patient indicates that coagulation had already occurred prior to thoracentesis. Clotting within the pleural cavity was followed presumably by the normal phenomenon of fibrinolysis or by the deposition of fibrin on the collapsed lung. No excessive fibrinolytic activity was found in the pleural blood, however. It has been postulated that the relatively intact pleural serous membranes might serve to keep the blood in a fluid state by virtue of some special property of these serous surfaces or even by the secretion of an anticoagulant at the site of the hemorrhage. Although it is possible that in some cases blood in the untraumatized pleural cavity may remain unaltered as regards coagulation, the present study offers evidence that

coagulation does proceed within the pleural cavity. Factors involved might include thromboplastin liberated by the breakdown of platelets, contact of the blood with foreign surfaces, and the agitation produced by respiratory movements. This clotting may be followed by the natural proteolytic process of fibrinolysis or by defibrination with fibrin deposition on the lung surfaces. At least in this patient, the so-called "incoagulable" hemothorax fluid was in reality serum which contained a suspension of some of the formed elements of the blood.—*Study of the coagulation mechanism of pleural blood in hemopneumothorax, S. W. Cosgriff, Am. J. Med., January, 1950, 8: 57.*—(*T. H. Noehren*)

Action of New Bronchodilator.—Experiments were carried out on canine heart-lung preparations with N-isopropyl-norepinephrine (Aludin, Alleidin, Isuprel, Neo-epenine, Neodrenal, and Norisodrene). Records were made of pulmonary arterial pressure, venous reservoir volume, and tidal air volume. The experiments show that on a weight basis this compound is 10 times more effective as a bronchodilator than epinephrine. Increases in tidal air volume were of the order of 5 to 10 per cent with 1.0 γ of the drug. This action was never complicated by a compensatory bronchoconstriction phase such as is seen with epinephrine. This was true whether the drug was inhaled or given intravenously. In addition, the compound caused a decrease in pulmonary artery pressure due to vasodilatation even after cocaine, atropine, and ergot; this was also in contrast to epinephrine and aminophylline. Both actions should improve the alveolar gas exchange in asthmatic patients.—*Vaso- and broncho-dilator effects of N-isopropyl-norepinephrine in isolated perfused dog lungs, C. O. Herb & H. Konzett, J. Pharmacol. & Exper. Therap., July 1949, 96: 228.*—(*S. Hadley*)

PUBLIC HEALTH AND EPIDEMIOLOGY

Tuberculosis in Yemenite Jews.—In Israel there are 4 ethnic groups of Jews: (*1*) the Ashkenazic group of European origin, (*2*) the Sephardic group from the mediterranean basin, (*3*) Oriental communities from southeastern Asia, and (*4*) the group from Yemen. The Yemenite Jews emigrated from an agricultural region where tuberculosis is almost unknown. In Israel this group has a tuberculosis rate 2.7 times that of the other Jewish groups and a mortality rate 5 times greater than theirs. It is suggested that long exposure of the Ashkenazim and Sephardim to tuberculosis in urban communities has allowed natural selection to increase the groups' resistance to the infection. This is further supported by the greater incidence among Yemenite Jews of such rapidly progressive forms as caseous pneumonia and miliary tuberculosis.—*Tuberculosis among Yemenite Jews in Israel (Hebrew), P. Wayl & J. Rakower, Harefuah (J. Med. Assn. Israel), June, 1949, 36: 1.*

Pulmonary Calcifications.—A detailed study of the correlation between the results of tuberculin and histoplasmin skin tests and the finding of pulmonary calcifications was made using data gathered in studies at 76 nursing schools in different metropolitan areas. The frequency of reactors to histoplasmin varied from 60 per cent in Kansas City, Missouri and Columbus, Ohio to less than 10 per cent in San Francisco, Denver, and Minneapolis. The incidence of tuberculin reactors varied from 23 per cent in Philadelphia to 8 per cent in Minneapolis. Pulmonary calcifications occurred in more than 20 per cent of the student nurses in Kansas City and Columbus and 5 per cent or below in San Francisco and Minneapolis. Among nurses with calcifications 68 per cent reacted to histoplasmin only, 13 per cent to tuberculin alone, and 14 per cent to both; only 5 per cent failed to react to either. In the reactors to histoplasmin alone there were 3 times as many calcifications as in the group that reacted to tuberculin alone. Only 0.7 per cent of those who reacted to neither skin test showed calcifications. This is further evidence that pulmonary calcifications may be related to histoplasma infections.—*Studies of pulmonary findings and antigen sensitivity among stu-*

dent nurses. IV. Relationship of pulmonary calcifications with sensitivity to tuberculin and to histoplasmin, J. C. Goddard, L. B. Edwards, & C. E. Palmer, Pub. Health Rep., July 1, 1949, 64: 820.—(*S. Hadley*)

Photofluorographic Survey in Greece.—A photofluorographic survey of 98,128 apparently healthy persons was conducted in Athens and the Salonica area of Greece between January 1946 and October 1947. The following results were obtained: (*1*) 1.30 per cent of 35,891 children and adolescents were found to have clinically significant pulmonary tuberculosis. (*2*) The incidence of clinically significant pulmonary tuberculosis in a group of 62,237 adults was 2.92 per cent. The mean age of this group was 31 years. (*3*) In the total of 98,128 examined, 2,291 were found to have clinically significant tuberculosis. Of these, 74.3 per cent were previously unknown cases. There were 65.4 per cent classified as cases for treatment and 34.6 per cent classified as cases for observation. (*4*) The curve of incidence is different in males and females. Whereas in males the curve rises steadily in proportion to age, in females variations occur and the peak incidence is noted in the 20- to 30-year age group. (Authors' summary)—*Photofluorographic survey in Athens and Salonica, B. Papanicolaou & Papastathopoulos, Acta tuberc. Scandinav., 1949, 23: 188,*—(*K. T. Bird*)

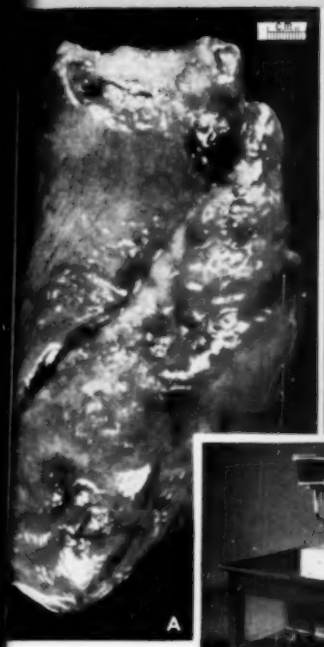
Tuberculosis Contact Survey.—An attempt was made to determine the potential case load of tuberculosis contacts who would require BCG vaccination. The territory surveyed was both industrial and rural and the observation period consisted of 6 quarter-years. A total of 159 tuberculous patients were found to have close contacts up to 14 years of age. Tuberculin tests were carried out on 253 (95.6 per cent) of these contacts. The number of nonreactors per quarter was tabulated as follows: (*1*) positive smear, 10; (*2*) positive culture, 3; (*3*) negative sputum, 12. Therefore a surprisingly large number of nonreactors was found. These required BCG, even if the source case was awaiting removal to a sanatorium.—*A survey of negatively reacting child contacts in relation to BCG vaccination, J. B. Shaw & N. Wynn-Williams, Tubercle, October, 1949, 30: 218.*—(*A. G. Cohen*)

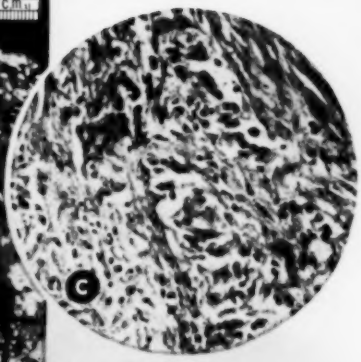
Tuberculin Skin Tests.—The statistical data of the Department of Medicine, University Hospital, Brno, were compared with data found in literature and with the results of tuberculin skin-testing performed on 300 healthy soldiers. The author concluded that Pirquet's test in adults is not sufficiently sensitive. Monrad's and Stewart's tests are much more sensitive but are often nonspecific. The best results were reported with the BCG test, which seemed more reliable than the tuberculin test itself. For practical use in adults a BCG test or a Mantoux test with increasing strengths of tuberculin is recommended.—*Tuberculin tests (Czech), J. Novak, Lekarské listy, 1949, 4: 418.*—(*J. Ilavsky*)

BCG Tuberculin Test.—Tuberculin was prepared from an eight-week-old culture of BCG grown on Sauton's protein-free synthetic medium. Old Tuberculin (OT) was used for comparison. Children were tested intracutaneously with similar amounts of each preparation and the results were read at 24, 48, and 72 hours. Induration of 5 mm. or more at 48 hours was considered positive. With a dilution of 1:10,000, of 91 children tested, 43 were positive and 48 were negative to both. In most, the positive reactions were more severe with OT. The 48 negative cases were retested with 1:100 tuberculin. Three were mildly positive, the others negative to both. There were less false positive reactions with the BCG tuberculin. Ten known reactors were tested with 1:100 OT, then with 1:100 BCG tuberculin. The reactions were much more severe with OT. It was concluded that BCG tuberculin is just as accurate as OT and is reliable and safe. It gives much less severe reactions and fewer pseudo-reactions. It may, with further research, become possible to employ only one test, using a dilution of BCG tuberculin between 1:1,000 (0.1 mg.) and 1:200 (0.5 mg.),

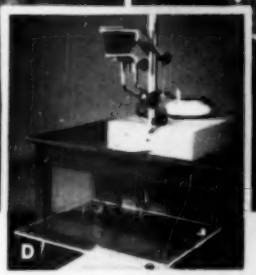
perhaps 1:500 (0.2 mg.).—*BCG tuberculin as a testing material, E. Friedman & I. Silverman, New England J. Med., December 8, 1949, 241: 894.—(A. G. Cohen)*

Possible Hazard of BCG.—It is now certain that BCG vaccination does not cause tuberculous infection. No death has been observed following such vaccination, and local discomfort or complications are rare. However, certain immunologic considerations arise. Injection of an antigen provokes a fall in the normal antibody titer in the blood. Such a fall or "negative phase" is also seen when an organism already possesses antibodies in the blood following an earlier infection. The clinical importance of this "negative phase" has been discussed particularly in connection with *Salmonella* infections and diphtheria. In spite of much work no agreement has been reached over the experimental, clinical, and epidemiologic findings. Theoretically, if infection occurs directly after BCG vaccination the ensuing tuberculous process might run a more serious course because of a transient diminution of resistance. Conversely, the vaccination of an individual already infected might increase the hazards because of an associated diminution of resistance. Previous investigations show that BCG vaccination of a tuberculin-positive organism does not entail any harmful effects but BCG vaccination of an actively tuberculous host may have an unfavorable effect. Accordingly groups of guinea pigs were inoculated with tubercle bacilli. Thereafter intracutaneous injections of BCG were given. These experiments failed to show that BCG vaccination had any harmful effect while the tuberculous process was moderate in extent. When the tuberculosis was advanced the pathologic changes might be interpreted as showing that BCG vaccination had produced an unfavorable influence. Nevertheless, a very extensive clinical experience indicates that there is no increased risk if BCG vaccination in humans is performed in the ante-allergic or in the tuberculin-positive stage.—*The possibility of a "negative phase" following BCG vaccination, J. Bøe, Acta tuberc. Scandinav., 1949, 23: 123.—(K. T. Bird)*





Reproductions **A** *and* **B** *show gross aspects of diseased lung after pneumonectomy. Reproduction* **C** *shows photomicrograph made from histological section of affected lung. Figure* **D** *shows setup of Kodak Flurolite Enlarger fitted with Camera components for the photography of gross specimens.*



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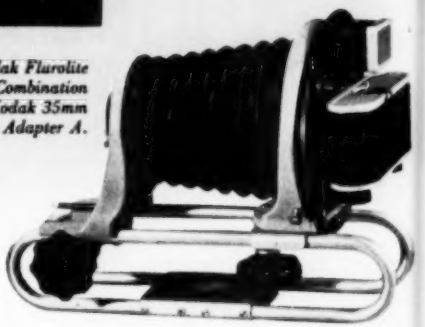

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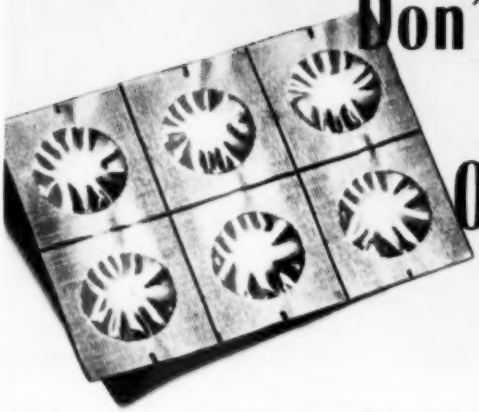

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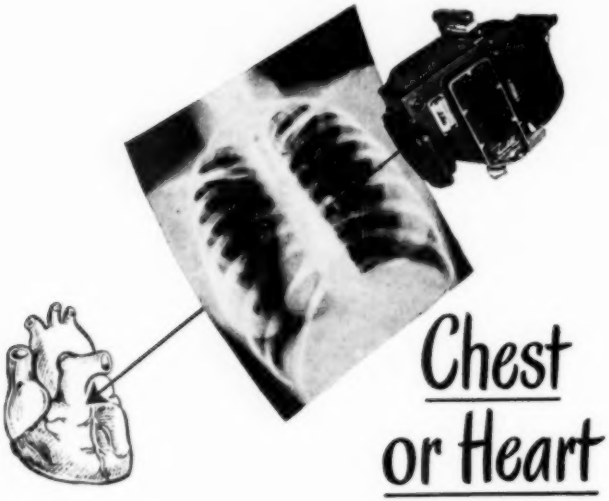

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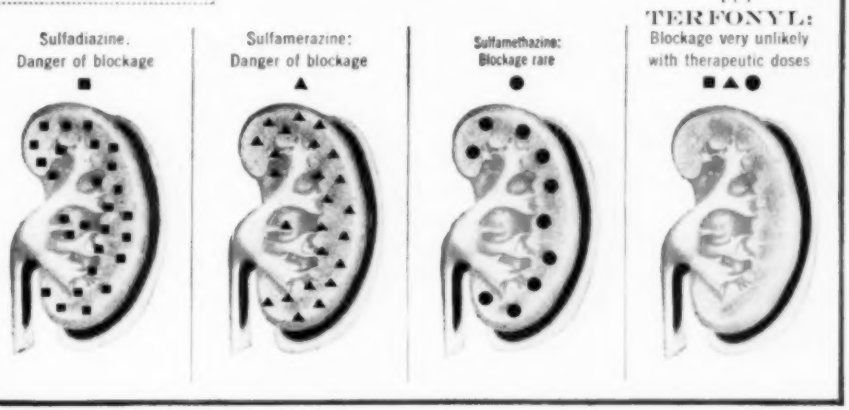

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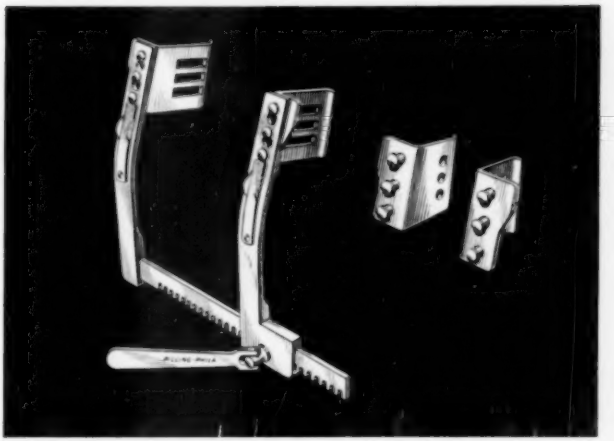

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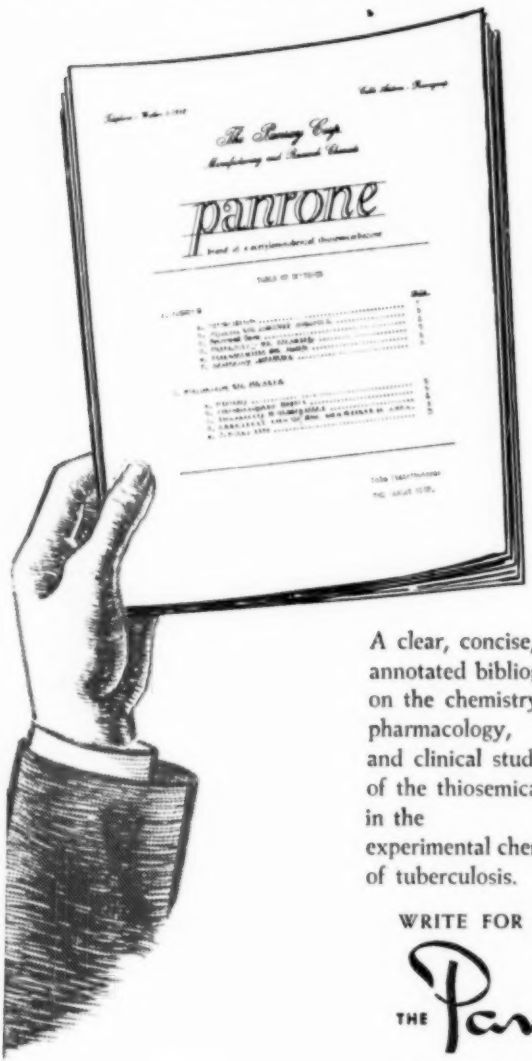

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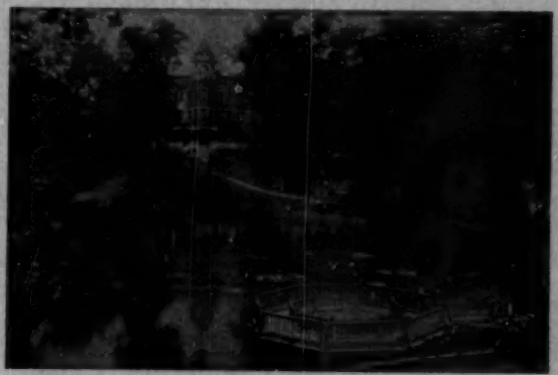

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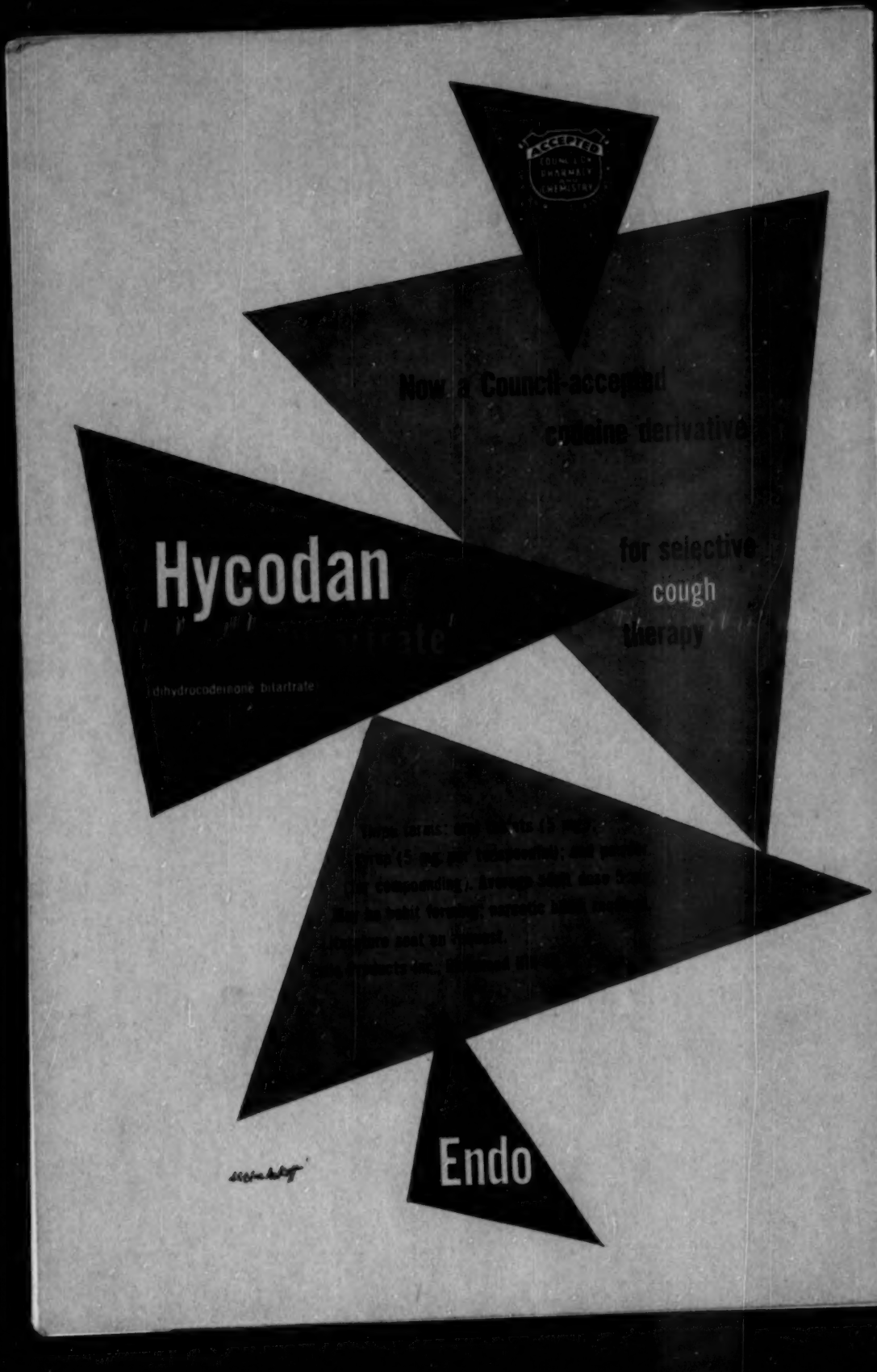
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